

REVIEW

Does consuming isoflavones reduce or increase breast cancer risk?

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Abstract

Epidemiological studies suggest that consumption of phytoestrogens, in particular isoflavones, correlates with a lower incidence of breast cancer. However, data from human intervention studies have been less clear. Several meta-analyses have reported beneficial but relatively weak effects of isoflavone consumption on reduction of hot flushes and osteoporosis and improvement of cholesterol levels. However, the effects of isoflavones on early breast cancer markers differ between pre- and post-menopausal women. Conclusions on whether exposure of animals (mice and rats) to isoflavones protects against or promotes breast cancer development and growth vary between different studies. These results, taken together with the heterogeneous outcomes of human interventions, have led to a controversy surrounding the intake of isoflavone to reduce breast cancer risk. Here, we describe the results of recent human and animal intervention studies and discuss factors that might explain the variation in results. We also describe possible molecular mechanisms of action of isoflavones; distinguishing which mechanism(s) are involved is needed if we are to solve the controversy surrounding the actions of these compounds.

Background

Phytoestrogens constitute a large group of naturally occurring compounds with a structural resemblance to estrogen. The two main subgroups of phytoestrogens, isoflavones and lignans, are present in foods such as soy, lentils, beans, chickpeas, whole-grain cereals, legumes and various vegetables and fruits, particularly berries. Following metabolism by colonic bacteria to more

biologically active metabolites, isoflavones and lignans show weak estrogen receptor (ER) binding activity and, depending on the context, they can act to either mimic or counteract the effects of endogenous estrogen, 17 β -estradiol.

High total lifetime exposure to estrogen correlates with an increased incidence of breast cancer. Thus, factors such as oral contraceptives, early puberty, late menopause and hormone replacement therapy are considered to be risk factors, whereas early childbirth and breastfeeding are known to consistently decrease lifetime breast cancer risk. Because phytoestrogens, and in particular isoflavones, can have both estrogenic and antiestrogenic effects, it has been suggested that they can modulate breast cancer risk. However, large quantities of contradictory results have been published on the topic. Here, we describe the heterogeneous results of recent human intervention studies and animal experiments on the effects of isoflavone on breast cancer risk. We discuss factors that might explain the variation in results and describe possible molecular mechanisms of action of isoflavones. To solve the controversy on the effects of isoflavones on breast cancer risk, it will be necessary to characterize tissue- and cell-specific actions of isoflavones (for example, in breast stem cells), and map the signaling pathways for different isoflavones.

Isoflavones in epidemiological and clinical studies

Although it is generally believed that phytoestrogens, especially isoflavones, can ease menopausal complaints, such as hot flushes and osteoporosis, and protect against cardiovascular disease, it has been difficult to generate consistent proof for this notion. A new meta-analysis [1] of 19 intervention reports concluded that there was a significant tendency in favor of finding that soy eased hot flushes, but also that there was great heterogeneity in the results of the published reports. The most recent meta-analysis on osteoporosis, which included data from 1,240 menopausal women, revealed that daily ingestion of soy isoflavone extract supplements for 6 to 12 months increased spine bone mineral density by 2.38%, but that no significant effects on femoral neck, hip total and trochanter bone mineral density were found [2]. Another

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meta-analysis, performed by the American Heart Association Nutrition Committee and including 22 randomized trials measuring cardiovascular endpoints [3], found that isoflavones decreased low-density lipoprotein cholesterol concentrations by approximately 3%, which was a small reduction relative to the large amount of soy protein tested (averaging a daily intake of 50 g). No significant effects on high-density lipoprotein cholesterol, triglycerides, lipoprotein(a) or blood pressure were found [3].

It has been even more difficult to determine whether isoflavones protect against or promote breast cancer. Most epidemiological investigations have found that soy intake is associated with a modest reduction in breast cancer risk ([4] and references therein). Several of these investigations were performed in Asian countries, and to what degree the results can be applied to women in the rest of the world, with different diets, sources of soy and genetic backgrounds, is not known. In fact, it was recently suggested that isoflavone intake is associated with a reduced risk of breast cancer incidence in Asian populations but not in Western populations [5].

The results of intervention studies of breast cancer and isoflavones are not uniform. A recent meta-analysis measuring breast density as an early biomarker of breast cancer risk concluded that isoflavone intake did not alter breast density in post-menopausal women but may have caused a small increase in breast density in premenopausal women [6]. This report [6] summarized different intervention studies in which women were treated with isoflavones or placebo for between 6 months and 3 years. Taken together, the intervention studies on correlating isoflavones to breast cancer risks are less conclusive than the epidemiological studies. Also, caution needs to be taken in the interpretation of the epidemiological studies in that they may have simply identified a 'healthy user effect' - in which the participants in the studies are more likely to have healthy lifestyles than the general population - and not reflected a direct effect of soy intake.

Isoflavones in animal studies

The reports on isoflavones in animal experimentation show both tumor-promoting and tumor-repressing effects. Several studies on rats conclude that the timing and duration of exposure is crucial for the effect. The incidence of chemically induced mammary tumors significantly decreased when prepubertal rats were exposed to soy extracts or the isoflavone genistein [7]. However, other studies report an increased tumor incidence following *in utero* and perinatal exposure to genistein. The data from mice are less clear, and reports have shown that exposure to genistein or soy had reduced, increased or had no effect on mammary tumor incidence and/or multiplicity and size [7]. The discrepancy in results may be explained partly by the fact that the rat and mouse

mammary gland tumor models differ; the rat models are carcinogen-induced and the mouse models oncogene-driven. However, in wild-type mice, unpublished data from our laboratory show that long-term exposure (45 to 90 days) of old mice to a low dose of genistein ($0.1 \text{ mg kg}^{-1} \text{ day}^{-1}$) resulted in immune cell infiltration in the kidney and pancreas, and may have led to liver lymphoma (Rodrigo Barros, personal communication). The immune cell infiltration was associated with a down-regulation of ER β expression. Thus, there might be a link between genistein consumption and tumor development in animals.

Another explanation for the discrepancies in results is that different animal studies (and also different human interventions) have used different sources of isoflavones. Many studies investigate whole soy extract (containing mainly the phytoestrogens genistein, daidzein and glycitein), whereas others use purified genistein, daidzein or equol, the gut bacterial product of daidzein. Other studies examine isoflavones from red clover, which contains mainly biochanin A and formononetin as well as small amounts of daidzein and genistein. Although all these compounds are classified as phytoestrogens, their activities are partly distinct. For example, opposite effects of different isoflavones have been reported; a recent study concluded that whereas genistein protected against tumor growth and metastasis of the MDA-MB-435 breast cancer cell line subcutaneously xenografted on nude mice, daidzein significantly promoted both tumor growth and metastasis [8]. The isoflavones also exert both ER-dependent and ER-independent effects (Table 1). Genistein, for example, does not only bind to and activate ER-driven transcription, but also inhibits the activity of tyrosine protein kinases, enzymes often over-expressed in cancer cells. The isoflavones may also act in concert; studies have shown stronger anti-tumorigenic effects of soy extracts, containing a combination of isoflavones among other substances, than of the isolated soybean constituents alone [9]. It must also be taken into account that constituents of soy extracts vary depending on the type of bean used to prepare it (such as yellow soybeans, black soybeans or sword beans) and on the growth conditions for the plant [10]. For instance, under fungal stress soybeans produce glyceollins, which have antiestrogenic activity [11]. There is thus currently no uniform definition of 'soy extracts', which makes it difficult to compare the results of different studies.

Isoflavone effects depend on molecular context

The heterogeneity in results described above may also depend on the fact that intervention studies do not compare the reported effects of isoflavones on early biomarkers of breast cancer with local estrogen levels in the breast tissue or with expression levels of ER α and

Table 1 Summary of the ER α -dependent and independent activities of genistein and isoflavones on signal transduction pathways

Compound	Effect	Test system*	ER α dependence	References
Genistein	Inhibition of tyrosine-specific protein kinase activity of EGFR, pp60v-src and pp110gag-fes	<i>In vitro</i> assay and A431 cells	Not assessed	[24]
Genistein	Inhibition of the MEK5/ERK5/NF- κ B pathway, leading to apoptosis	MDA-MB-231 cells	ER α -independent	[25]
Genistein	G2/M-phase cell cycle arrest through activation of phosphorylated ERK1/2	MDA-MB-231 cells	ER α -independent	[26]
Genistein	Downregulation of the PI 3-kinase/Akt signaling pathway, leading to inhibition of estrogen-induced proliferation	MCF7 cells	ER α -dependent	[27]
Genistein	Repression of HER2 protein expression, phosphorylation and <i>HER2</i> promoter activity	BT-474 cells transfected with either ER α or ER β	Both ER α -dependent and independent effects	[28]
Genistein	Inhibition of proliferation and induction of apoptosis in <i>BRCA1</i> mutant cells through p21CIP/WAF and Akt. Cells with wild-type <i>BRCA1</i> were more resistant to effects of genistein	MDA-MB-231 cells (wild-type <i>BRCA1</i>); HCC1937, SUM149 and SUM1315 cells (mutated <i>BRCA1</i>)	Not assessed	[29]
Genistein	Activation of cell growth through increased IGF-1 receptor gene expression	MCF-7 cells	Both ER α -dependent and independent effects	[30]
Isoflavones	AR, PR and PPAR γ binding and activation	<i>In vitro</i> ligand binding assay, yeast transcription activation assay	ER α -independent	[31]

*Cell lines: MCF-7, an ER α -positive breast tumor line; MDA-MB-231, an ER α -negative breast tumor line; MCF-10a, an ER α -negative fibrocystic breast cell line; HCC1937, SUM149 and SUM1315, breast cancer cell lines with mutated *BRCA1*; BT-474, a breast cancer line; A431, an epidermoid carcinoma line. Other abbreviations: AR, androgen receptor; *BRCA1*, breast cancer 1; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; HER2, human epidermal growth factor receptor 2; IGF-1, insulin-like growth factor 1; MEK, mitogen-activated protein kinase/extracellular signal-regulated kinase; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; p21CIP/WAF, cyclin *kinase* inhibitor p21; PI, phosphatidylinositol; PPAR γ , peroxisome proliferator-activated receptor gamma; PR, progesterone receptor; pp60v-src, protein kinase encoded by the transforming gene (*v-src*) of Rous sarcoma virus; pp110gag-fes, tyrosine kinase encoded by the transforming gene (*v-fes*) of Feline sarcoma virus.

ER β . In theory, the effect of isoflavones would vary from being antiestrogenic to weakly estrogenic depending on whether the women have high or low endogenous estrogen levels (which are generally 50 to 400 pg/ml in premenopausal women and 10 to 20 pg/ml in postmenopausal women); an assumption based on studies of transgenic mice with 'estrogen response element'-driven expression of a luciferase reporter gene [12]. When these mice were ovariectomized (to not produce endogenous estrogen) and given soy-based feed, luciferase activity was increased in the liver, pituitary and mammary gland, indicating an estrogenic response to soy. On the contrary, when the mice first were injected with estrogen, soy feed attenuated estrogen-induced luciferase expression [12]. A meta-analysis of 47 studies suggested that soy or isoflavone consumption did not affect levels of estrogen in pre- and post-menopausal women, but significantly reduced follicle-stimulating hormone and luteinizing hormone in premenopausal women [13]. These studies suggest that isoflavones do not alter estrogen concentrations at a systemic level; rather, isoflavones would modify the response to estrogen locally. Whether isoflavones also could modify local estrogen metabolism in breast tissue or not is not known.

The action of isoflavones can also be predicted to depend on the ER α /ER β ratio of the target organ. Although both receptors are estrogen- and isoflavone-induced transcription factors, the physiological consequences of

ER β -mediated transcriptional regulation are distinct from those of ER α . For example, whereas ER α signaling is proliferative and important for development of female breast tissue, ER β is non-proliferative, do not have a stimulating effect on the mammary gland and may counteract the actions of ER α . Thus, isoflavones may induce proliferation or reduce proliferation depending on the ER context, which rarely, if at all, has been investigated in soy intervention studies. Being more selective for ER β , isoflavones would mainly reduce proliferation, but that is true only for individuals who express high enough levels of ER β in breast tissue.

Insights from genomic studies

New hopes for shedding light on the tumor-preventing capacity of isoflavones come from genomic studies. So far, these have mainly been performed on cell culture models, in which the ER α /ER β ratio can be regulated. A recent report on T47D breast cancer cells showed that genistein induced transcriptomic and proteomic signatures that indicate rapid cell growth and migration by dynamic activation of cytoskeleton remodeling in the presence of ER α only [14]. When both ER α and ER β were expressed, the ER α -mediated effects were counteracted and genes and proteins involved in cell growth were downregulated, whereas cell cycle arrest and apoptosis factors were induced. A study using two breast tumor cell lines (MCF-7, which is ER α positive, and MDA-MB-231,

which is ER α negative) and a fibrocystic breast cell line (MCF-10a, ER α negative) showed that 278 and 334 genes were differentially expressed in ER α -positive cells compared with ER α -negative cells after genistein and daidzein exposure, respectively [15]. This demonstrates that the two isoflavones partially regulate compound-specific target genes, and that they affect both ER α -dependent and -independent transcriptional regulation [15].

It has also been suggested that genistein may alter the epigenetic pattern, such as the pattern of genomic DNA methylation, as other estrogens do, which in turn may alter the dynamics of growth in breast cancer cell lines [16,17]. Also, in animal models there is evidence that maternal exposure to genistein affects methylation patterns in the offspring [7], although the consequences of the epigenetic change for breast cancer risk is not known. It should be noted that *in utero* exposure to environmental estrogen-mimicking pollutants, such as bisphenol A, also induces methylation changes in rat pups, and that the exposed mice have an increased incidence of hyperplasia (although this has mostly been studied in the male prostate) [18].

Effects of estrogen on breast stem cells

A recent and important finding in the breast cancer field is that normal breasts and breast cancers both contain breast stem cells. These stem cells are characterized by self-renewal capacity, and they express stem-cell-associated genes. Surprisingly, treatment with estrogen inhibits expression of stem-cell genes and reduces the number of mammospheres (clusters of cells formed by culture of breast stem cells under non-adherent non-differentiating conditions), but it increases the sizes of the individual mammospheres [19]. This indicates that estrogen reduces the pool of self-renewing stem cells, most likely by promoting their differentiation and simultaneously escalating the proliferation of more differentiated progenitors. As increased numbers of progenitors or stem cells have been suggested to be linked to increased breast cancer risk, estrogens would have both tumor-promoting and -repressing functions at the same time. However, the manner by which isoflavones affect breast stem cells and progenitors has not yet been addressed, and neither has the ER α /ER β ratio in these cell populations.

Future outlook and conclusions

Although epidemiological studies suggest that isoflavones can decrease both breast cancer risk and even increase survival of breast cancer patients [20,21], the intervention studies and animal experiments are not as conclusive. We can at least say that for post-menopausal women there are no serious adverse effects following the consumption of soy isoflavones for a limited period of time [22,23].

However, for younger women, children and women with a genetic predisposition for breast cancer, the ratio between beneficial and adverse effects remains to be elucidated.

To solve the controversy of isoflavone consumption on breast cancer risks, new intervention studies that analyze whether decreased breast cancer risk correlates with isoflavone levels, local hormone levels and ER α /ER β ratio are needed. Furthermore, the effects of isoflavones on mammary gland stem cells during different periods of life need to be defined to identify windows of time in which isoflavones can have positive or negative effects on cancer prevention. Investigations of the effect of isoflavones on breast cancer stem cells would increase our knowledge of whether isoflavones are beneficial or not to cancer patients. Lastly, the possibility that isoflavones have different effects on breast cancer risks between different ethnic groups with different genetic backgrounds needs to be taken into account. Addressing these issues will be an important step toward reaching consensus on whether or not to consume isoflavones to reduce breast cancer risk.

Abbreviations

ER, estrogen receptor.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

The authors contributed equally to the writing of this manuscript. The unpublished data that are presented were produced in the research group of J-AG.

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