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Qiu S, Jiang C. Soy and isoflavones consumption and breast cancer survival and recurrence: a systematic review and meta-analysis. Eur J Nutr. 2019 Dec;58(8):3079-3090.

What We Know, Think We Know, or Are Starting to Know

While we now know the importance of bioactive components of foods, in particular flavonoids, ask a nutrition professional to list flavonoid-rich foods and they are likely to go with dark pigmented fruits, wine, and perhaps cacao and dark chocolate. Soy is seldom conjured to mind when we think of flavonoids, yet the isolfavones found in soy are in fact a flavonoid subclass.

Soy foods, in particular soybeans, tofu, and fermented soy products like tempeh and miso, are the most common source of isoflavones in the human diet [(1)]. The main isoflavones in soy products are known as daidzein, genistein, and glycitein, and these compounds - daidzein and genistein in particular - differ from other flavonoids subclasses in one important characteristic: they are *phytoestrogens*.

Phytoestrogens are plant ['phyto'] compounds which are structurally similar to 17-beta estradiol, an oestrogen sex-steroid hormone produced by the ovaries during the reproductive phase of the lifespan [(2)]. These phytoestrogens bind to oestrogen receptors, and may therefore have oestrogenic and anti-oestrogenic effects [(2)]. In particular, a compound known as equol* [a non-steroidal oestrogen] is produced from daidzein by gut bacteria, and equol has greater affinity for binding to the oestrogen receptor [(3)].

There are two types of oestrogen receptors [ER]: ER-alpha [ERα] and ER-beta [ERβ] [(4)]. ERα are expressed more in the mammary gland and uterus, while ERβ are expressed more the central nervous and immune systems, and counteract against cell hyper-proliferation [i.e., the growth rate of cells, highly relevant to the growth of cancers] induced by ERα [(4)]. Of note, soy isoflavones have greater affinity for ERβ, thus it is proposed that this increased ERβ binding may act as an antagonist to ERα-mediated cell growth [(5)].

Breast cancer [BC] can be subdivided according to whether the tumour cells express ERα or not [(6)]. If the cells *do* express ERαa, this is known as 'ER-positive' BC, and if they *do not*, this is known as 'ER-negative' BC [(6)]. This is important, because when ERα-positive cells bind to circulating oestrogen, it stimulates tumour growth [(5,6)].

Soy isoflavones have garnered interest for their potential benefit in hormone-dependent cancers like BC. The proposed mechanism is that soy isoflavones act as phytoestrogens, which are mildly oestrogenic and in binding to the ER, result in lower oestrogen production, thereby inhibiting cell proliferation.

*Geek Box: Phytoestrogens and Equol

While soy is generally recognised for the phytoestrogen activity of its main isoflavones, it is the metabolism of daidzein to equol that may be of particular interest for the purported health effects of soy foods. Before they can be fully absorbed, soy isoflavones are metabolised by gut bacteria; this is a step that is now recognised as a critical stage in metabolism and ultimate bioactivity of all (poly)phenolic compounds. It is important to note that equol is not a phytoestrogen, yet is is often misclassified as such in the literature. Equal is exclusively a product of bacterial metabolism of daidzein, and does not appear in urinary excretion [its elimination pathway] unless soy foods are produced in the diet. Equol is a non-steroidal oestrogen, which can be drugs [e.g., tamoxifen] or naturally occurring compounds that may exert oestrogenic activity. In this regard, while genistein and daidzein have affinity for binding to the ERβ receptor, the affinity for equol is much greater, and equol exerts greater antioxidant activity compared to the precursor isoflavones. In this regard, it appears that between genistein and daidzein, genistein has significantly greater affinity for the ER-beta receptor [greater than tamoxifen]. Thus, the purported activity of daidzein may be predicated upon conversion to equol. Due to the modifying effect of the gut microbiota, the concept of an "equol producer" has been identified, although the definition appears to be relatively arbitrary. It may be a combination of genetics and the background diet, however, East Asian populations exhibit greater equol-production capacity compared to Western populations. It has been suggested that equol provides more of a plausible mechanistic explanation for the association between soy foods consumption and lower risk of chronic diseases, compared to the precursor soy isoflavones. If this is the case, the distinction between "equol producers" and "non-producers" may provide an explanation for certain of the inconsistencies in the literature. Future studies should seek to quantify equol producing capacity as a critical potential effect modifier.

The Study

The investigators conducted a systematic review with the following inclusion criteria:

- Exposure of interest was soy foods and/or soy isoflavones
- Soy food/isoflavone intake was assessed either before or after a diagnosis of BC
- The outcome of interest was:
    - Overall survival [OS, i.e., mortality among women with BC]
    - Breast-cancer specific survival [BCSS]
    - Recurrence of cancer
- The study reported relative risks [or hazard ratios] with 95% confidence intervals [CI]

The included studies were also combined into a meta-analysis. The study investigated specific subgroup analyses, to investigated the effects of the following variables on the outcome: menopausal status, ER status, tumour stage, smoking, physical activity, and whether participants were receiving treatment. As certain studies reported on soy foods generally, while others reported specifically on soy isoflavones, a separate analysis also investigated the associations between soy isoflavones alone and BC.

Results: 12 studies were included in total; 10 prospective cohorts, 1 case-control study, and 1 pooled analysis of three cohorts. The average follow-up duration across all studies was 6.3yrs, during which a total of 5,770 total mortality cases, 2,386 BCSS mortality cases, and 1,500 BC recurrences, were documented.

- ***OS*:** In analysis of 8 studies which reported on OS and pre-diagnosis soy and isoflavone intake, the highest [compared to lowest] was associated with a significant 16% [HR 0.84, 95% CI 0.71 - 0.98] lower risk of mortality.
- ***BCSS*:** In analysis of 5 studies which reported on BCSS and pre-diagnosis soy and isoflavone intake, the highest [compared to lowest] was associated with a non-significant 11% [HR 0.89, 95% CI 0.74 - 1.07] lower risk of mortality.
- ***BC Recurrence*:** In an analysis of 2 studies which reported on pre-diagnosis soy and isoflavone intake and BC recurrence, the highest [compared to lowest] was associated with a significant 27% [HR 0.73, 95% CI 0.60 - 0.87] lower risk of recurrence. A single study [which was a pooled analysis of 3 cohorts of both US and Chinese women] that reported on post-diagnosis intake showed a significant 25% [HR 0.75, 95% CI 0.61 - 0.92] lower risk of recurrence.
- ***Subgroup Analyses*:**
  - **Menopausal Status:** In analysis of 5 studies which reported on OS and soy and isoflavone intake relative to menopausal status, the highest [compared to lowest] was associated with a significant 19% [HR 0.81, 95% CI 0.67 - 0.99] lower risk of mortality.
  - **ER Status:** In analysis of 4 studies which reported on OS and soy and isoflavone intake relative to ER status, there was stronger effect noted for ER-positive women with a non-significant 24% [HR 0.76, 95% CI 0.56 - 1.04] lower risk of mortality, compared to ER-negative women which showed a 10% [HR 0.90, 95% CI 0.65 - 1.24] lower risk that was not significant.
  - **Isoflavones:** In analysis of 7 studies which reported specifically on soy isoflavone intakes and OS, the highest [compared to lowest] was associated with a significant 19% [HR 0.81, 95% CI 0.66 - 0.99] lower risk of mortality. This was non-significant for BCSS [HR 0.92, 95% CI 0.76 - 1.12]

There were no significant findings in relation to other variables and either OS or BCSS outcomes.

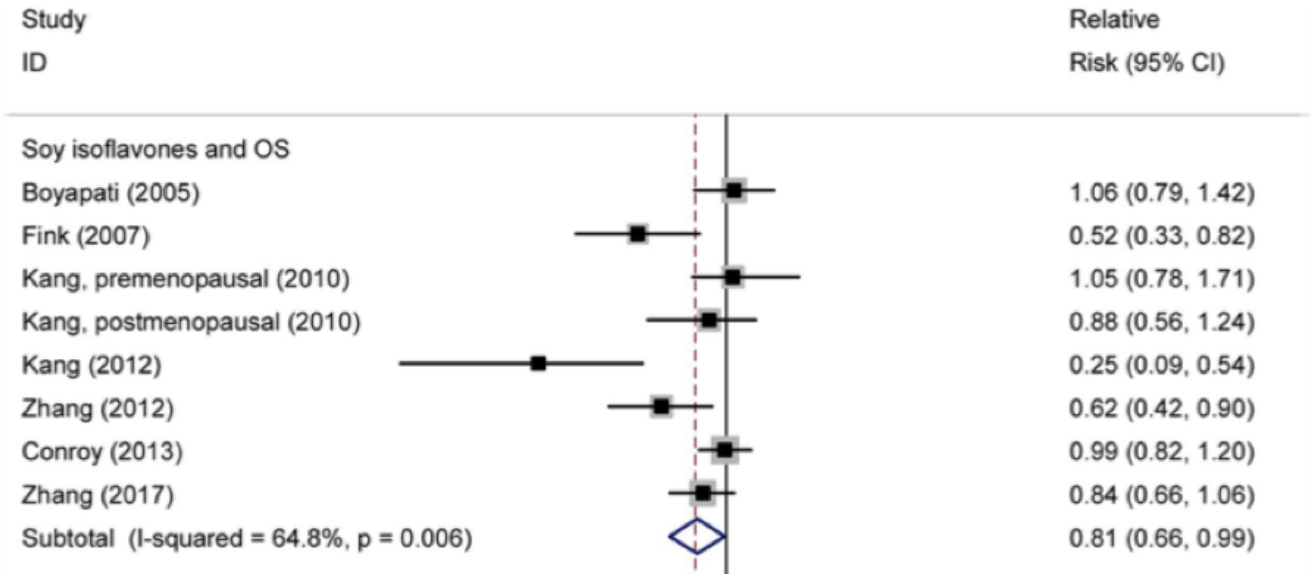

Figure *from paper illustrating the association between soy isoflavone intake and OS [i.e., survival time to overall mortality], showing that higher isoflavone intake was associated with lower risk of mortality, however, this was not significant for breast cancer survival, which could relate to the fact that only 4 studies specifically investigated this relationship.*

The Critical Breakdown

Pros: Relevant databases were searched up to 2018, providing the most [until then] inclusion of studies meeting the inclusion criteria. The included studies combined for a large sample size, with a substantial number of recorded outcomes. The included studies were also recent publications, spanning the period 2005 to 2017. This included 5 updated publications that had not been included in the previous meta-analysis on the topic. The subgroup and meta-regression analyses [see ***Key Characteristic***, below] provided further insights into potential effect modifiers.

Cons: The main 'Con' is becoming almost generic to nutrition meta-analysis; the "distortive lumping" of exposures, which which ranged from soy products generally, to different levels of isoflavones, to miso soup alone. Insofar as isoflavones themselves are the putative mechanism by which soy foods may benefit BC-related outcomes, the range of isoflavones and different background diets in populations studied could explain some of the heterogeneity between studies. The authors noted that publication bias was observed in their analysis. Publications were confined to English language only, which given regional differences in soy consumption and associated research, may have excluded some potentially relevant literature.

Key Characteristic

This update analysis, which included 5 publications from 2013 to 2017, allowed for a more sophisticated subgroup and meta-regression analysis to tease out potential variables that may influence any observed associations. In the subgroup analysis, the effects of a specific variable on the outcome are analysed separately, for example, this study [in addition to the factors in the Results like menopausal and ER status] looked at study location [Asia vs. Western], study setting [population vs. hospital], clinical BC state, treatment, smoking, physical activity, for the effects that each of these may have on overall survival. It allowed for an important finding to be teased out; that while there was an overall lower risk in the main analysis, this was primarily driven by lower risk in postmenopausal women.

The meta-regression analysis took the subgroup analysis one step further. A meta-regression analysis is an extension to a subgroup analysis, which takes the effect estimate in the primary analysis [i.e., the hazard ratio for the association with OS and BCSS], and adds multiple variables into a predictive model to see if any of these variables may predict the observed association between the exposure [soy and isoflavones] and outcomes. While the subgroup analysis takes each of these variables in isolation, meta-regression analyses these factors simultaneously. In the present study, none of the variables listed above significantly influenced the finding between higher soy intake and the modest risk reduction for mortality.

Interesting Finding

Although this finding was not statistically significant, the lower risk observed in ER-positive women compared to ER-negative women is interesting because it is the *opposite* of other findings. In a 2019 meta-analysis, Nachvak et al. found that soy isoflavones were associated with a 23% [HR 0.77, 95% CI 0.60 - 0.99] lower risk of BC mortality in ER-negative BC, but no effect was found in ER-positive BC [7]. The relationship between soy isoflavones and ER-negative may be considered to have more biological plausibility; isoflavones have greater affinity for the ER-beta receptor, as does the isoflavone metabolite equol [3,8]. This would be expected to induce ER-beta and counteract the effects of ER-alpha induced tumour growth [5]. However, a recent analysis found relatively no difference in risk of BC from isoflavone intake between ER-positive and ER-negative types [9]. Thus, whether the effects of soy and isoflavones are mediated by ER type remain to be fully clarified.

Relevance

There are perhaps a number of levels at which to think the associations between soy and isoflavones and BC risk through on: a) the overall risk reduction; b) the magnitude and precision of effect, and c) effect modifiers like menopausal status, etc.

In relation to a) and b), the overall body of evidence is suggestive of a lower risk with higher soy and isoflavone intakes, however, the effect is modest in magnitude and weak in precision. The Nachvak et al. [7] meta-analysis, based on a similar pool of studies included in the present analysis, found that a 10mg/d increase in soy isoflavones was associated with a 9% [HR 0.91, 95% CI 0.84 - 0.99] lower risk of BC mortality. Micek et al. [9] found a 16% [HR 0.84, 95% CI 0.74 - 0.97] lower risk of overall mortality in BC patients. Thus, whether looking at overall mortality in BC patients or BC-specific mortality, the magnitudes of effect in the Nachvak et al. [7] and Micek et al. [9] studies, and the precision of the effect size based on the confidence intervals, are relatively similar to the present study. Thus, the overall body of evidence would suggest a very modest effect on BC risk.

In relation to c), however, it may be that the associations with soy isoflavones and BC are more evident in postmenopausal women, and the magnitude and precision of effect stronger in relation to BC recurrence. With regard to menopausal status, both the present study and the Micek et al. [9] study found similar 19% and 17% reductions in mortality risk, respectively, in postmenopausal women. With regard to BC recurrence as an outcome, the present study found a 27% lower risk of recurrence, and the Micek et al. [9] study also found a 27% [HR 0.73, 95% CI 0.64 - 0.84] lower risk of BC recurrence. The Micek et al. analysis included one additional study to the present analysis, which did not change the outcome as the magnitude of effect remained the same, and the precision of the effect estimate was practically the same. Taken together, the most robust finding in terms of effect estimate and confidence intervals appears to be the lower risk of BC recurrence.

However, the ultimate caveat is that between differential effects of soy foods vs. isoflavones specifically, the potential modification by ER type and receptor activity, and differences in the levels of isoflavones and stage of the lifespan in which soy consumption occurs, there are no conclusive interpretations of the literature in relation to soy and isoflavones and BC risk possible at this juncture.

Application to Practice

If a true effect of soy and/or isflavone intake in relation to BC risk exists, at this point the effect is modest and lacks the desired robustness to make definitive recommendations. Nonetheless, it is a broadly healthy food group that is a feature of notable healthy dietary patterns, and its inclusion for women [and for men!] adds nutrients or bioactives associated with positive health outcomes, in particular soy protein and isoflavones. From the perspective of BC, there is still a number of key variables to tease out as discussed above. While there is no apparent reason to discourage the inclusion of soy foods in women at risk of BC, a point I feel quite strongly about with diet and cancer: in the hierarchy of treatment needs it is a lesser decisive factor compared to chemo/radiotherapy and other treatment options. It is unlikely to harm, it may help, but it won’ t remit.

References

1. Zaheer K, Humayoun Akhtar M. An updated review of dietary isoflavones: Nutrition, processing, bioavailability and impacts on human health. Critical Reviews in Food Science and Nutrition. 2015;57(6):1280-1293.
2. Sirotkina A, Harrath A. Phytoestrogens and their effects. European Journal of Pharmacology. 2014;741(15):230-236.
3. Setchell K, Brown N, Lydeking-Olsen E. The Clinical Importance of the Metabolite Equol—A Clue to the Effectiveness of Soy and Its Isoflavones. The Journal of Nutrition. 2002;132(12):3577-3584.
4. Paterni I, Granchi C, Katzenellenbogen J, Minutolo F. Estrogen receptors alpha (ERα) and beta (ERβ): Subtype-selective ligands and clinical potential. Steroids. 2014;90:13-29.
5. Poschner S, Maier-Salamon A, Zehl M, Wackerlig J, Dobusch D, Pachmann B et al. The Impacts of Genistein and Daidzein on Estrogen Conjugations in Human Breast Cancer Cells: A Targeted Metabolomics Approach. Frontiers in Pharmacology. 2017;8.
6. Allred D, Brown P, Medina D. The origins of estrogen receptor alpha-positive and estrogen receptor alpha-negative human breast cancer. Breast Cancer Research. 2004;6(6).
7. Nachvak S, Moradi S, Anjom-shoae J, Rahmani J, Nasiri M, Maleki V et al. Soy, Soy Isoflavones, and Protein Intake in Relation to Mortality from All Causes, Cancers, and Cardiovascular Diseases: A Systematic Review and Dose–Response Meta-Analysis of Prospective Cohort Studies. Journal of the Academy of Nutrition and Dietetics. 2019;119(9):1483-1500.e17.
8. Kuiper G, Lemmen J, Carlsson B, Corton J, Safe S, van der Saag P et al. Interaction of Estrogenic Chemicals and Phytoestrogens with Estrogen Receptor β. Endocrinology. 1998;139(10):4252-4263.
9. Micek A, Godos J, Brzostek T, Gniadek A, Favari C, Mena P et al. Dietary phytoestrogens and biomarkers of their intake in relation to cancer survival and recurrence: a comprehensive systematic review with meta-analysis. Nutrition Reviews. 2020;79(1):42-65.