Editor’s Note: The relationship between soy and health has been rigorously investigated for 30 years. Approximately 2,000 soy-related peer-reviewed articles are published annually. Soy research covers everything from the role of soy in meeting nutrient requirements to improving skin health. Author Mark Messina, chairman of The Soy Connection editorial board, examines 6 trending topics below.

**SOY OIL, PROTEIN AND HUMAN HEALTH**

By Mark Messina, PhD, MS

**Soy and Breast Cancer Survivors**

The position of the American Cancer Society, the American Institute for Cancer Research and the World Cancer Fund International is that breast cancer survivors can safely consume soyfoods. In fact, the latter organization concluded that post-diagnosis soy intake may improve the survival of breast cancer patients, a conclusion consistent with the epidemiologic data. Chi et al. meta-analyzed the results of 5 prospective studies, 3 from China and 2 from the U.S., and found that among the >11,000 women with breast cancer, soy intake reduced recurrence and mortality by a statistically significant 26% and 16%, respectively. More recently, Qiu and Jiang meta-analyzed a similar dataset and found reductions in risk of similar magnitudes, but the findings were not quite statistically significant.

In 2015, after a multi-year comprehensive review of the literature, the European Food Safety Authority (EFSA), which is analogous to the U.S. Food and Drug Administration (FDA), concluded that isoflavones do not adversely affect breast tissue. This conclusion was also arrived at by the Permanent Senate Commission on Food Safety of the German Research Foundation—the organization that first raised concerns about isoflavones and requested that the EFSA review the data. Their conclusions are consistent with clinical studies showing isoflavones do not affect markers of breast cancer risk, such as mammographic density and breast cell proliferation.

Concerns about the impact of soyfoods on women with breast cancer are based on the similarity between isoflavones and the hormone estrogen, and studies in mice that began to be published in the late 1990s by researchers from the University of Illinois. However, isoflavones differ from estrogen at the molecular level in that they preferentially bind to estrogen receptor beta (ERβ) in comparison to estrogen receptor alpha (ERα), whereas estrogen has equal affinity for both receptors. Activation of ERβ is generally seen as having antiproliferative effects and as countering the stimulatory effects of ERα activation. Rodent studies are certainly a legitimate part of the scientific literature, but their limitations are well documented. This limitation is especially true in the case of soy, because rodents metabolize isoflavones differently than humans. Furthermore, not all rodent studies show isoflavones stimulate the growth of estrogen-sensitive mammary tumors.

Rodent studies also raised concern that isoflavones would interfere with the efficacy of tamoxifen. This concern is supported by the results of a recent study by Deng et al., who found that among premenopausal women with luminal A breast cancer, soy intake was linked with the downregulation of genes associated with sensitivity to tamoxifen. However, in 2014, Shike et al. found that even though soy intake upregulated genes associated with breast cell proliferation, such proliferation was not increased. Thus, gene expression as we understand it does not fully predict biological response. Furthermore, prospective epidemiologic data show that soy intake does not inhibit the efficacy of tamoxifen.

Despite the overall encouraging data and the positions of prestigious scientific organizations, the soy and breast cancer controversy has not been definitively resolved. Resolution would require conducting a large, multi-year trial in which women with breast cancer are randomly allocated to a soy group or a control group and recurrence and/or mortality are determined. No such trial has been conducted, nor does it appear that one is planned; although given the epidemiologic data, one is arguably warranted.

Nevertheless, given that the clinical data are supportive of safety and the epidemiologic data suggestive of benefit, a reasonable position is that soyfoods can be part of
an overall healthful diet for breast cancer survivors. As to the amount, the largest prospective study, which was included in the meta-analyses by Chi et al. and Qiu and Jiang, and involved >5,000 survivors, found that consuming even 25g soy protein per day was associated with reduced breast cancer recurrence and mortality. However, in the 4 other prospective studies, soyfood consumption was much lower. Therefore, 2 servings per day would appear to be a reasonable intake goal.

**Soy and Thyroid Function**

There is a long history of research into the effect of soy on thyroid function. In the 1960s, several cases of goiter were attributed to the use of soy infant formula; however, this problem was soon eliminated when the formula began to be fortified with iodine. In the 1990s, in vitro research showed that isoflavones could inhibit the activity of thyroid peroxidase, a key enzyme involved in the synthesis of thyroid hormones. Although this inhibition was also shown to be the case in rats, thyroid function remained normal. In 2006, a comprehensive narrative review that included 14 clinical trials found the totality of the evidence showed that neither soyfoods nor isoflavones adversely affect thyroid function in euthyroid men or women. Studies published since this review, which include 2 that were 3 years in duration are supportive of this finding. In addition, the EFSA concluded that isoflavone supplements do not affect thyroid function in postmenopausal women—a position consistent with the Permanent Senate Commission on Food Safety of the German Research Foundation and the FDA.

Soyfoods may increase the amount of thyroid medication needed by hypothyroid patients, not because of an effect on the thyroid, but because soy protein may interfere to some extent with the absorption of levothyroxine. Soy is not unique in this regard, however, as many herbs, drugs, fiber, and calcium supplements have similar effects. In any event, it is not necessary for thyroid patients (with the exception of infants with congenital hypothyroidism) to avoid soyfoods since thyroid medication is taken on an empty stomach and dosages can easily be adjusted to compensate for any effects of soy.

There is concern that soy may worsen thyroid function in those whose thyroid function is compromised such as subclinical hypothyroid patients and those whose iodine intake is marginal. The concern about the latter is based on the potential for isoflavones rather than the amino acid tyrosine to be iodinated, thereby inhibiting the synthesis of thyroid hormone. However, clinical research published in 2012 indicates that the iodination of isoflavones is negligible and clinically irrelevant.

Finally, 2 British studies conducted by the same research group examined the effect of soy on thyroid function in subclinical hypothyroid patients. The first found that isoflavone exposure (16mg/day) increased the likelihood of progressing from subclinical to overt hypothyroidism. This finding is unexpected given the low dose of isoflavones used (1 serving of a traditional soyfood contains approximately 25mg isoflavones), the progression of subclinical to overt hypothyroidism among Japanese patients is not elevated, and the rates of hypothyroidism in Japan are not elevated. Furthermore, isoflavone exposure caused marked and statistically significant reductions in systolic and diastolic blood pressure, insulin resistance, and inflammation (as assessed by C-reactive protein); these effects were much larger than typically seen in other studies.

In contrast to this study, a follow-up study conducted by the same research group published 7 years later that used a much larger dose of isoflavones (66mg/day), failed to find an effect of isoflavones on the progression of subclinical hypothyroidism. The results of this study cast some doubt about the findings of the initial study.

**Effects of Soy on Male Hormones**

The notion that because soyfoods contain isoflavones they feminize men was popularized by a 2009 article in *Men’s Health*. Six years later the magazine rejected this claim, but the damage had been done. Two case reports describing feminizing effects that likely occurred as a result of soyfood consumption have been published. However, in both cases the individuals were estimated to consume 360mg/day isoflavones (~9-fold greater than the mean intake among older Japanese men), in the context of unbalanced and likely nutrient-deficient diets in which soyfoods accounted for most of the calories consumed. Instead of 12 servings per day of soy, if these men had consumed 12 servings of milk, beef, liver, or Brazil nuts, they would have exceeded the safe upper limit for calcium, iron, vitamin A, and selenium, respectively. The 2 aforementioned case reports simply illustrate that consuming excessive amounts of essentially any food can lead to abnormalities.

More importantly, a systematic review and meta-analysis that included 15 placebo-controlled treatment groups with baseline and ending measures and an additional 32 reports involving 36 treatment groups, found no effects of soy protein or isoflavone intake on testosterone, sex hormone binding globulin, free testosterone, or the free androgen index. Subsequently published studies support this finding. Similarly, a narrative review that included 9 studies found neither soy nor isoflavones affect circulating estrogen levels in men. Subsequently published studies support this finding. As somewhat of an aside, a recently published meta-analysis found that soy protein supplementation produces similar gains in strength and lean body mass in response to resistance exercise training as animal protein, including whey protein.

**Soybean Oil (and full-fat soyfoods) and Inflammation**

A common misperception is that omega-6 polyunsaturated fat (PUFA), which is found in abundant amounts in most oils, including soybean oil, is pro-inflammatory. Conversely, it is thought that omega-3 PUFA is...
anti-inflammatory. Since chronic inflammation is believed to be a key process underlying many chronic diseases, it is important to understand the impact of fat on inflammation.

For decades, the thinking has been that linoleic acid, the main dietary omega-6 PUFA, is pro-inflammatory because in vivo it can be converted to arachidonic acid, a fatty acid from which several downstream pro-inflammatory metabolites (e.g., eicosanoids) are produced. Conversely, the downstream metabolites of the long-chain omega-3 fatty acids, specifically docosahexaenoic acid (DHA), are thought to be anti-inflammatory.

The above reasoning has led to recommendations regarding the optimal dietary ratio of omega-6 to omega-3 fatty acids. Some experts think that the ideal ratio could be as low as 1:1,7 which is clearly much lower than the current U.S. dietary ratio of approximately 10:1.74 However, in recent years, recommendations for consuming a diet with a specific omega-6:omega-3 ratio have been abandoned by the Institute of Medicine,75 U.K. Food Standards Agency,76 Food and Agriculture Organization of the United Nations,77 and the American Heart Association (AHA).78

Current thinking is that in vivo, the extent to which dietary linoleic acid is converted to arachidonic acid is extremely limited.79 Furthermore, it is now appreciated that some of the downstream metabolites of arachidonic acid are anti-inflammatory.80 These observations likely account for why a systematic review of clinical trials concluded that there is “virtually no evidence” from clinical trials that linoleic acid, the main dietary omega-6 PUFA, increases concentrations of inflammatory markers in healthy people.81

There is still the issue of the inhibitory effect of linoleic acid intake on the conversion of alpha-linolenic acid to eicosapentaenoic acid (EPA) to consider.82 However, according to the AHA, because this conversion is already quite low,83 it is not clear that additional small changes would have net effects on CHD risk after the other benefits of linoleic acid consumption are taken into account. The position of the AHA, like that of the FAO, is that the focus should not be on ratios but rather on intake levels of each type of essential fat.84 Decreasing linoleic acid intake as a means of increasing the dietary ratio of linoleic acid to alpha-linolenic acid as some have called for,85-87 could very well have the opposite effect of that intended.78

New research shows that the response to the dietary intake of linoleic acid is modified by polymorphisms in the fatty acid desaturase (FADS) gene cluster.88 The delta-5 and delta-6 desaturases enzymes are involved in the desaturation and elongation of linoleic acid and alpha-linolenic acid. Although speculative, genotype may end up dictating the response to linoleic acid.

Finally, although the impact of omega-6 and omega-3 fatty acids on health is often discussed in regard to heart disease, a new pilot trial shows these fatty acids potentially affect a diverse array of health outcomes.89 For this trial, breast cancer patients suffering from fatigue as a result of their treatment were randomly assigned to consume daily for 6 weeks either 6g of fish oil, 6g of soybean oil, or 3g each of soybean oil and fish oil. At study termination, all groups experienced a reduction in fatigue; however, contrary to expectations, the reduction in the soybean oil group was significantly greater than the reduction in the fish oil group. Furthermore, the reduction was correlated with a decrease in inflammation. The reduction in the combined supplement group was intermediate between the 2 other groups.

**Soy and the Microbiome**

Microbiome and microbiota are often used interchangeably. However, microbiota refers to the microorganisms found in an environment; while the microbiome refers to the collective genomes of microorganisms inhabiting a particular environment. Research into the effect of the microbiome on health has absolutely exploded. To this point, in the year 2000, there were only 79 articles related to the microbiome indexed in PubMed whereas, in 2010 and 2018, there were 1,168 and 1,831 articles, respectively. Although much is to be learned about the microbiome, a recent review highlighted the evidence suggesting that dietary modulation of the microbiome is an emerging therapeutic option for a variety of different diseases.90 The relationship between soyfoods and the microbiome has been studied to only a limited extent but there are several ways in which this relationship is relevant to the health effects of soyfoods.

Much of the carbohydrate in soybeans is comprised of oligosaccharides, such as raffinose, but especially stachyose.91-95 These sugars are largely non-digestible in the gut due to the absence of α-galactosidase in the human intestinal mucosa. The soybean oligosaccharides are classified as prebiotics as they have been shown to increase the growth of bifidobacteria.96-99 Members of the genus Bifidobacterium are generally viewed as being advantageous to the host.100 Fermented soyfoods may have an especially large impact on the microbiota and microbiome. For example, based on their research, Kuligowski et al.101 speculated that one of the mechanisms by which tempeh prevents diarrhea is by stimulating the growth of certain intestinal microflora groups. Also, Fujisawa et al.102 found that the consumption of miso soup containing natto increased the numbers of Bacillus and Bifidobacterium and decreased the number of Enterobacteriaceae and Clostridium perfringens; all changes which are considered beneficial.

In addition to the oligosaccharides, other components of soybeans, including both the protein and fat, may affect the microbiome. Huang et al.103 concluded that the changes in the microbiota in
response to soy consumption are consistent with reported reductions in pathogenic bacteria populations in the gut, which should lead to beneficial effects on health.

Finally, isoflavone metabolism varies markedly among individuals; most notable in this regard is that only about 25% of non-Asians and 50% of Asians host the intestinal bacteria that convert daidzein into the isoflavonoid equol. In 2002, Setchell et al. proposed that those individuals who host these bacteria are more likely to benefit from soyfood consumption. Whether diet can change the microbiome such that a non-equol-producing individual is converted into an equol-producing one remains to be definitively determined. However, results from a recently published cross-sectional study reported that daidzein intake was associated with higher numbers of bacteria capable of producing equol, which suggests that chronic soy consumption could lead to non-producers of equol becoming equol producers.

Soy and Cognitive Function

Research into the effects of soy on cognitive function got off to a bit of an alarming start. In 2000, results from a cross-sectional study of Japanese men living in Hawaii—the Honolulu–Asia Aging Study—showed that those men who ate the most tofu exhibited more signs of mental decline in their 70s through their 90s compared to those who consumed less. However, the study was not designed to look specifically at cognitive function, and it had numerous methodological weaknesses. In the years since that study was published, other research has shown mixed results on soyfoods and cognition. After comprehensively reviewing the animal, clinical, and epidemiologic data, Soni et al. concluded in 2014 that “the evidence to date is not sufficient to make any recommendations about the association between dietary intake of soy iso-flavones and cognition in older adults.”

While that conclusion is still very much relevant, 2 recently published studies suggest soy intake may exert cognitive benefits. One is an epidemiologic study that included 1,105 Taiwanese participants aged 65 and over who completed the Short Portable Mental Status Questionnaire (SPMSQ), which measured cognitive function. All participants also provided extensive information on their dietary habits by filling out a food frequency questionnaire and by indicating the foods they consumed within the past 24 hours.

After adjusting for a wide range of potentially confounding variables in comparison to not consuming soy, those who ate soy less than 1 time per day were 43% (relative risk, 0.57; 95% confidence interval: 0.32, 1.03) less likely to be cognitively impaired and those eating soy at least daily were 55% (relative risk, 0.45; 95% confidence interval: 0.25, 0.81) less likely to be cognitively impaired. The latter finding was statistically significant.

In the other study, Zajac and colleagues enrolled moderately vitamin B12-deficient men and women aged 45 to 75 years (n=56) in a randomized controlled crossover trial. Participants (55% female) consumed 50g whey protein or soy protein isolate daily for 8 weeks. Following a 16-week washout phase, they consumed the alternative supplement. Consumption of whey protein significantly improved vitamin B12 and folate status but did not result in direct improvements in cognitive function. In contrast to whey, among the women in the study, soy protein statistically significantly improved reaction time and reasoning speed.

Zajac et al. speculated that the isoflavones in soybeans were responsible for the observed cognitive benefits because the benefits were observed only in women and most of the women were postmenopausal.

**Editor’s Summary:** The health effects of soyfoods have been rigorously investigated for 30 years. This research covers a wide range of topics. The attention granted to any given area waxes and wanes according to the latest findings. Dr. Messina’s article has addressed those topics that in recent years have generated considerable debate and discussion. In the coming years, a whole new set of topics may rise to the forefront. This newsletter will continue to monitor the literature and social media so that we can provide you with the soy information that best meets your needs.

**REFERENCES**


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