American Institute of Cancer Research says soy is safe for breast cancer survivors

Following an extensive review of the scientific literature, the American Institute of Cancer Research (AICR) concluded that soyfoods can safely be consumed by women who have had breast cancer. According to AICR nutrition advisor Karen Collins, MS, RD, “Determining whether it is safe for breast cancer survivors to eat soy has been one of the big research questions under study and now we know it is safe—the evidence is so consistent,” Ms. Collins also noted that “… for breast cancer survivors who want to eat less meat, get protein and enjoy a more plant-based diet, soy is a healthy food and everyone—including breast cancer survivors—can feel comfortable eating it.” The AICR conclusion is not surprising since it is not even clear estrogen increases breast cancer risk. (See conclusion of U.S. Preventive Services Task Force Recommendation Statement, page 4.)


The AICR is one of the nation’s largest cancer charities, focusing exclusively on the link between diet and cancer. The AICR supports innovative research in cancer prevention and treatment at universities, hospitals and research centers across the US, and has provided millions of dollars in funding for research in diet, nutrition and cancer.

Isoflavones and hot flash onset: Media misleads

A new epidemiologic study of the relationship of soy iso-flavones to hot flash incidence has received widespread media attention despite the fact that the study fails to provide meaningful data. The study objective was to determine whether isoflavones or fiber prevent the onset of hot flashes in a multi-ethnic sample of American women. This prospective cohort, the Study of Women’s Health Across the Nation (SWAN), has produced a number of useful findings related to diet and health, but those findings don’t include relevant outcomes related to isoflavones.

In the latest report, 3,302 pre-menopausal and early perimenopausal women, 1,651 of whom
reported no vasomotor symptoms (VMS, e.g., hot flashes) at baseline were followed with annual visits for 10 years. Dietary intakes of isoflavones and fiber were assessed by a food frequency questionnaire at baseline and at annual visits 5 and 9 and interpolated for intervening years. The number of days experiencing VMS in the past 2 weeks was self-reported annually.

While the researchers found no relationship between soy isoflavone intake and hot flash incidence, this wasn’t especially surprising. That’s because average intake of isoflavones among the women was less than one milligram per day. Such a low intake wouldn’t be expected to produce any relevant effects. In contrast, a 2012 meta-analysis of 17 clinical studies found definitive evidence that an isoflavone intake of 50 milligrams per day alleviates both hot flash frequency and severity. That’s the amount of isoflavones provided by 1½ to 2 servings of soyfoods per day, and is 100-fold greater than the average isoflavone intake in the SWAN cohort. As a result, the SWAN study provided no meaningful information about the relationship of isoflavones or soy intake to hot flash incidence.

Previous reports from this study found that average intake among even the Chinese- and Japanese-American women, who comprised 15% of the SWAN cohort, was only about 10 milligrams of isoflavones per day. Among those in the highest intake group in the current analysis, daily isoflavone intake for Chinese and Japanese women ranged from only about 13 to 26 milligrams, well below the amounts shown to be effective in preventing hot flashes.

There were additional limitations to this study. VMS were classified according to the number of days per two-week period they were experienced: none, 1 to 5 days, or 6 days or more in the past two weeks. But, while isoflavones reduce the frequency and severity of symptoms, in most instances they don’t completely eliminate hot flashes. (Nor does estrogen therapy for that matter.) Women who experience fewer hot flashes or less severe hot flashes overall in response to either estrogen therapy or isoflavone intake could still be expected to experience them as many days as before. Beneficial effects regarding fewer hot flashes per day would have been missed in the SWAN study.

Finally, even if isoflavones do prevent the onset of hot flashes, this benefit would be of questionable value. Hot flashes typically occur around the time of menopause, which is commonly defined as one year without menses, although they can begin two years before menopause. In Western women, menopause generally occurs around the age of 50 although there is about a 10 year range for when menopause occurs. Therefore, if a woman wanted to use isoflavones to prevent the onset of hot flashes, she would need to start consuming isoflavones at the age of 45 or so and conceivable take them for as many as 10 years. This is a long time to take a supplement to alleviate a condition that might not even arise when it is possible to simply begin using isoflavones to alleviate hot flashes once they start.

Unfortunately, in their discussion, the authors of the current analysis didn’t cite the low isoflavone intake of the women in their cohort as a weakness of their study. Nor did any of the media reports on this study. In 2004, a letter to the editor of the American Journal of Clinical Nutrition argued that Western epidemiologic studies involving the general population have little chance of providing insight into the health effects of isoflavone-rich foods, because of the low isoflavone intake of these populations. The SWAN study exemplifies that point.

 Isoflavones reduce menopausal symptoms and lower lipid levels

Canadian researchers recently completed a two-year clinical trial evaluating the health effects of isoflavones alone and in combination with exercise in over 300 postmenopausal women. Women consumed 105 mg of isoflavones daily (Novasoy, Archer Daniels Midland) with or without exercise (a resistance training and walking program). A fourth group was given a placebo. Results indicated that isoflavones and exercise each individually maintained hip bone mineral density (BMD) relative to the placebo. This finding is in contrast to several previous long-term trials that have failed to find beneficial effects of isoflavones on BMD in postmenopausal women. Also, unexpectedly, the combination of exercise and isoflavones in this study actually adversely affected hip BMD. There were no effects of either treatment or the combination on lumbar spine BMD.

On the other hand, isoflavone supplementation was effective for improving leg strength (i.e. hack squat strength) and, both isoflavones alone and combined with exercise significantly lowered LDL-cholesterol by approximately 6% (~0.21 mmol or ~8 mg/dl). Isoflavone supplementation also reduced adverse reports of menopausal symptoms compared to non-isoflavone groups (14% vs. 33%; p = 0.01). Menopausal symptoms that were classified as adverse events included breast tenderness, decreased concentration, depression, fatigue, hot flashes, insomnia, numbness, vaginal dryness, vaginal itching, night sweats, subjective weight gain, migraine headaches, anxiety, irritability, and changes in bleeding patterns.

It isn’t clear why the combination of isoflavones and exercise adversely impacted hip BMD, but it is important to note that a previous study reported that this combination favorably impacted hip BMD more than either treatment alone. Consequently, at this point it is not possible to reach a conclusion about an interaction between isoflavones and exercise on hip BMD.

Finally, and very importantly, isoflavone supplementation did not affect two measures of safety, endometrial thickness and mammographic density. Endometrial thickness and mammographic density assess risk of endometrial and breast cancer, respectively. These results agree with a large dataset showing isoflavones don’t affect these markers. One limitation of this study is that compliance with the isoflavone or placebo supplement was low; 70, 65, 74, and 64% for the exercise, isoflavone, isoflavone and exercise and control groups, respectively. Overall, the results of this two-year trial support the benefits of isoflavone supplementation. Isoflavones were shown to be safe, lowered LDL-cholesterol, improved leg strength and reduced adverse reports related to menopausal symptoms.

Soy safety evaluated

The EU-funded Benefit-Risk Assessment of Foods (BRAFO) project has developed a framework for the quantitative comparison of human health risks and benefits in relation to foods and food compounds. According to the BRAFO methodology, the first step sets the scope of the assessment and describes the benefits and risks potentially involved in a particular exposure situation. In regard to the review of soy:

THE POTENTIAL BENEFITS ARE:
1. Reduced breast cancer risk
2. Reduced prostate cancer risk
3. Improved bone health (osteoporosis)
4. Reduced cardiovascular disease risk
5. Improved cognitive functions.

THE POTENTIAL RISKS ARE:
1. Disruption of sex hormone levels and changes in reproductive function
2. Impaired thyroid function
3. Increased breast cancer risk
4. Impaired cognitive function.

The evidence for the above effects are derived from (a) epidemiology studies that are based on soyfood consumption estimated either by dietary assessment or by urinary/blood isoflavone measurements and (b) intervention studies using soyfoods or isoflavone supplements.

CONCLUSIONS AT TIER 1

It is apparent that the alternative scenario (consuming 25 g/d soy protein versus current European soy intake) involves both potential benefits and potential risks compared with the reference scenario. However, the evidence for benefits is derived mostly from epidemiology and human intervention studies. Furthermore for each of these beneficial outcomes there have been sufficient studies to conduct meta-analyses, so the quality of evidence is in many cases “probable” or even “convincing.” In contrast the data on risks are mostly derived from animal models and are usually not supported by data from human studies. As a result, the quality of evidence ranges from “insufficient” to “possible.” It is also important to note that the magnitude of the beneficial and adverse effects is considered to be at best moderate, but in most cases low or very low.

CONCLUSIONS AT TIER 2

The beneficial effects clearly dominate the potential risk. It is not advised to go to tier 3 since the overall health impact is negligible. The alternative scenario would result in an overall benefit for the general adult population.

Genistein and brain estrogen levels

Women are diagnosed with Alzheimer’s disease (AD) at a greater rate than men, which is partially associated with a sharp reduction in estrogen levels during menopause. AD pathology is characterized by deposition of β-amyloid peptide (Aβ), which is generated from amyloid precursor protein (APP) by β-secretase (BACE1) and γ-secretase activity. To investigate whether a shortage of brain estrogen alters sensitivity of the response to estrogen replacement therapy and genistein, an international team of researchers used different animal models to examine estrogen and genistein treatment in AD neuropathology. Treatment with both estrogen and genistein reduced brain amyloid levels by increasing Aβ clearance in mice with a genetic deficiency that results in the brain containing nondetectable levels of estrogen as well as in ovariec- tomized mice whose brains contain very low estrogen levels. This study also revealed that early treatment with estrogen or genistein induced attenuation of Aβ in mice with normal levels of brain estrogen through

“There is adequate evidence that the use of estrogen alone results in a small reduction in the risk for developing or dying of invasive breast cancer.”

From the U.S. Preventive Services Task Force Recommendation Statement on Menopausal Hormone Therapy for the Primary Prevention of Chronic Conditions (Annals of Internal Medicine, Moyer et al., October 25, 2012)

continues on page 5
upregulation of nephrilysin, an enzyme that degrades a number of small secreted peptides including Aβ. The same treatments were also beneficial in mice with low estrogen levels by downregulating BACE1. Finally, early treatment (age 3 months) was much more effective than beginning treatment at age 12 months. The authors suggest that “early and long-term usage of estrogen and/or genistein may prevent AD pathologies in a dependent manner on endogenous brain estrogen levels in aged females.”


### Statbite

Dietitians use and recommend dietary supplements: Report of a survey (n=300)

<table>
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<tr>
<th>Dietary Supplement</th>
<th>Percent of Registered Dietitians Using in Previous Year</th>
<th>Frequency of Supplement Use</th>
<th>Percent of Dietitians</th>
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<tr>
<td>Multivitamin</td>
<td>84</td>
<td>Any current use</td>
<td>96</td>
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<tr>
<td>Calcium</td>
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<td>Regular use</td>
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<td>Omega-3/fish oil</td>
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<td>Occasional use</td>
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<th>Reasons for Supplement Use</th>
<th>Percent of Registered Dietitians Who Recommend Supplements to Clients</th>
<th>Percent of Registered Dietitians Who Use Supplements</th>
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<td>Lower cholesterol</td>
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<td>Women’s health (menopause)</td>
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Source: Dickinson et al., Nutrition Journal 2012, 11:14