ALTERNATIVE THERAPIES IN WOMEN'S HEALTH

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INSIDE

Soy Protein and Breast Cancer

By Lynn Keegan, RN, PhD, HNC, FAAN, and Gerald T. Keegan, MD, FACS

SOYBEAN PROTEIN AND OTHER PHYTOESTROGENS HAVE BEEN POPULARIZED in the lay press both as being preventives for breast cancer as well as for treatment of menopausal symptoms. The scientific evidence for these effects is not clear and, at times, is confusing. Because of the lower incidence of both hot flashes and breast cancer in Asian women than women of other racial origins, a hypothesis has emerged in the scientific community suggesting that the lower incidence of both these phenomena might be related to the increased consumption of isoflavone-containing soy products in the Asian diet.[1] The results of scientific investigations have been contradictory. Although most animal studies have shown a relationship between soy protein consumption and breast cancer preventive effects, a few studies have suggested that soy phytoestrogens may stimulate breast cancer cell growth under certain circumstances.[2] Whether phytoestrogens have any effect at all in humans is debated and the data are still unclear.

A related dilemma recently has developed for women who take estrogen/progestin compounds for the prevention of menopausal symptoms. Results from the Women's Health Initiative[3] and the long-term follow-up of the Heart and Estrogen/Progestin Replacement Study[4] show an increased risk of both cardiovascular disease and breast cancer among women randomized to hormone therapy.[5] For this reason, many women are seeking alternatives to prescribed estrogen/progestin compounds and have started using dietary supplements containing isoflavones derived from soy protein and red clover.[6,7] A recent study suggests that although isoflavones can have some biological activity, the substances tested in this study had no clinically important effect on hot flashes or other menopausal symptoms.[8]

Constituents and Metabolism

An annual legume of the Fabaceae or Legumenosae family (*Glycine max.*), soybeans originated in Asia, have been cultivated widely for more than 2,000 years, and have been widely consumed by more than a fourth of the world's population.[9] Products derived

from soybeans include tofu, miso, and soy milk. These products contain several different classes of phytoestrogens. The three main classes are the isoflavones, coumestans, and lignans.[10] Some of these agents are thought to have antioxidant, antibacterial, anti-angiogenic, antiproliferative, and antiparasitic effects, but only four (genistein, daidzein, biochanin, and formononetin) have potent phytoestrogenic activity.[10] Little data are available on the quantitative absorption, protein-binding, or the specific metabolism of dietary estrogens. It is known that dietary phytoestrogens are metabolized by intestinal bacteria, absorbed and then conjugated in the liver, circulated in the plasma, and excreted in the urine.[11]

There are no data on the developmental effects in humans of soy protein. This leads one to question whether the age of the individual at the initiation of a phytoestrogen-rich diet will affect the eventual effect of phytoestrogens on breast cancer prevention, and whether intake at an early age specifically will condition the receptors.[11] One study supporting results of immigration and epidemiological studies concluded that soy protein might be beneficial in the prevention of breast cancer, but only if consumed in early life or in adolescence.[10,12] This is confirmed by a study that measured soy protein intake and breast cancer risk in Asian women of mixed origin during adolescence and adulthood. Subjects who were high consumers during adolescence and adulthood showed the lowest risk. The risk was intermediate in those who were high consumers during adolescence and low soy consumers during adult life. The risk did not appear to be different between those who were low consumers during adolescence and high consumers during adulthood, leading to the conclusion that high soy intake during childhood among Asian-Americans is associated with reduced breast cancer risk.[13]

Proposed Mechanisms of Action as a Modifier of Breast Cancer

Isoflavones are polyphenolic compounds that are structurally related to estrogens. These so-called phytoestrogens bind to estrogen receptors[14] and have greater affinity for estrogen receptor beta than alpha.[15] These agents also may act as partial agonists in some tissue and antagonists in others, which leads to the conclusion that these compounds may exert tissue-specific effects. The postulation that these agents might be effective for breast cancer prevention at least partially is contingent upon the presence, quantity, and type of estrogen receptor in tissue with the potentiality of developing into cancer in high-risk individuals. If this is their sole mechanism of action, phytoestrogen compounds would not be expected to have any impact on the 30% of breast cancers that are estrogen receptor-negative.[16]

The effect of soy protein may be more complex and is mediated only partially by the alteration of estrogen receptors.[17] Photochemicals also may act synergistically as demonstrated in the induction of cellular growth arrest in response to DNA damage (GADD) produced by a combination of dietary-available indole-3-carbinol (I3C) with genistein.[18] This demonstration of synergism suggests the possibility that the preventive dietary effects noted in specific Asian populations may not be related to a single agent, but rather may result from different dietary components acting together. The effects of soybean genistein were compared with a commercially available isoflavone soy extract containing several different soy proteins to determine the effect on the growth of F3II mouse mammary adenocarcinoma cells.[19] The study concluded that the inhibition of cell growth, although noted in both groups, was of greater magnitude in the genistein-containing soy extract cohort than in the group receiving an equivalent amount of genistein alone. The study also concluded that this was due in part to the specific effects on the specific cell cycle regulatory proteins.

Another example of interaction is seen between

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A Guide to Soyfoods

Soymilk is made from the whole soybean. The creamy liquid varies in color from tan to white. It is lactose- and casein-free and is available in regular and low-fat varieties. Some brands are fortified with calcium, vitamin D, and/or vitamin B_{12}.

Soy Flour is made by grinding roasted soybeans into a fine powder. Soy flour is available in both full-fat (contains the natural oils found in the bean) and defatted (in which the oils are removed during processing) forms. Although both full-fat and defatted soy flour adds protein to recipes, the defatted soy flour adds more because the protein is more concentrated.

Soy Protein Powder can be added to recipes to boost the protein content. Soy protein isolate is a dry powder made from defatted soy flakes. It contains 90% protein, which is the highest amount for any soy product, and all the essential amino acids of soy products. Soy protein isolate often is labeled "soy protein powder drink mix."

Soy Meat Alternatives, or meat analogs, are made when soy protein is mixed with other ingredients to simulate various kinds of meat. Soy meat alternatives are created to look and taste like meats, but do not actually contain any meat at all. Available flavors include pork, beef, poultry, and sausage.

Whole Green Soybeans that are harvested at 80% maturity are called edamame. This special variety of soybeans is bigger and sweeter than most commercially grown soybeans. Edamame is served cooked and salted for a snack, and also can be used in recipes.

Whole Dry Soybeans are fully mature and dry when harvested. Once these beans are cleaned, they must be soaked and cooked before using in recipes. Soybeans should be cooked before eating so that the protease inhibitor found in soybeans is destroyed. Cooking also improves the digestibility of the beans.

Textured Soy Protein is made when defatted soy flour or soy protein concentrate is compressed and extruded into granules. The granules are rehydrated with water, which gives textured soy protein a texture similar to ground beef.

Tempeh is a chunky soybean cake made when whole soybeans are mixed with another grain (such as rice) and fermented into a cake of soybeans with a smoky or nutty flavor.

Adapted from: U.S. Soyfoods Directory. *2003 Soyfoods Guide*. Available at www.soyfoods.com. Accessed Aug. 19, 2003.

phytoestrogens and vitamin D. A steroid hormone derived from vitamin D(3)—1,25-dihydroxyvitamin D(3) (1,25(OH)(2)d(3))—is known to be a negative growth regulator of breast cancer cells. Reservadol, a soy-derived phytoestrogen, has been shown to sensitize breast cancer cells to the growth inhibitory effects of vitamin D.[20]

Another postulated mechanism of action involves the generation of reactive oxygen species (ROS). The effect of fermented soy protein was tested on several different human breast cancer cell lines and was found to have an inhibitory effect. The inhibitory effect seemed to be caused by the additive effect of a wide variety of constituents and actual cell apoptosis occurred. Growth inhibition and ROS generation induced by the fermented soy protein was inhibited by catalase and deferoximine, indicating that ROS was the cause of cell apoptosis.[21] Studies in cell culture also have demonstrated that genistein-induced inhibition of cell division is mediated partly by decreased telomere length, reduced mitosis, and inhibition of Akt activation, leading to induction of apoptosis.[22]

Clinical Studies

Breast cancer prevention trials studied several different allopathic agents. The two most common agents are tamoxifen and raloxifene. Tamoxifen has been demonstrated in five different studies to reduce the risk of estrogen receptor-positive breast cancer.[23] Tamoxifen is a non-steroidal anti-estrogen. The anti-estrogen may be related to its ability to compete with estrogen for binding sites in target tissue. In animal models, tamoxifen appears to exert its antitumor effects by binding estrogen receptor sites, and in in vivo experiments tamoxifen has been found to compete with estradiol for estrogen-receptor protein.[24] However, a significant incidence of uterine malignancies, both adenocarcinoma and uterine sarcoma as well as stroke and pulmonary embolism, has been found in high-risk women using tamoxifen in breast cancer prevention trials.[24] For this reason, the use of this drug has not been advocated extensively except in very high-risk individuals.

There is perhaps more hope for the use of raloxifene. The actions of raloxifene also are mediated by estrogen receptors, but in some cases raloxifene will activate certain estrogenic pathways and in others it will produce a blockade, acting as an agonist in some receptors and as an antagonist in others. The technical term for this class of agents is a selective estrogen receptor modulator (SERM). Raloxifene apparently blocks and does not stimulate the estrogen receptors in breast and uterine

Table 1

Protein Content in Various Soyfoods

Soyfood	Soy Protein Content
4 oz tofu	13 g
1 soy sausage link	6 g
1 soy burger	10-12 g
8 oz plain soymilk	10 g
1 soy protein bar	14 g
1/2 cup tempeh	19.5 g
1/4 cup roasted soy nuts	19 g

Source: U.S. Food and Drug Administration. Adding soy protein to the diet. Available at: http://vm.cfsan.fda.gov/~dms/fdsoypr.html. Accessed Aug. 19, 2003.

tissue, yet it will decrease the absorption of bone and reduce biochemical markers of bone turnover in postmenopausal women to premenopausal levels.[25] For this reason raloxifene has been considered safe for the prevention of osteoporosis in women at high risk for breast cancer and more recently its effectiveness in the prevention of breast cancer has been studied. The results of those studies have not as yet been compiled. Raloxifene also carries the risk of significant side effects including thromboembolic complications.[16] Both tamoxifen and raloxifene are very expensive.

Another class of agents being tried in breast cancer prevention is the aromatase inhibitors (AI). These agents have fewer side effects than tamoxifen or raloxifene, inhibit estrogen synthetase, and potentially offer the benefit of reducing the catechol estrogen metabolites, which play a role in the initiation of breast carcinogenesis.[26]

Ideally, a chemopreventative agent used in an otherwise healthy population should be effective, nontoxic, safe for long-time use, convenient, inexpensive, and have minimal side effects. The fact that soy proteins may act as either agonists or antagonists at the level of the estrogen receptor and may act as SERMs leads us to speculate that these proteins will act in preventing breast cancer in the same way as is postulated for raloxifene, yet not carry the side effects or the expense.

A study in China demonstrated that cell apoptosis in breast cancer cell lines (MCF-7 and T47D) was induced by genistein in a manner similar to that of tamoxifen.[27] It is possible that a naturally occurring, inexpensive, dietary substance with minimal side effects might work as well as the more expensive and toxic agents in the prevention of breast cancer. However, the results of studies in human subjects have been inconsistent and somewhat discouraging. For example, one Chinese study comparing the dietary choices of 200 women with breast cancer with adequately matched controls suggested that soy product intake had a protective effect in premenopausal women but no effect in the postmenopausal group.[28] Another similar study in China found no statistically protective effect of soy protein in either pre- or post-menopausal women.[29] However, a relationship clearly was established in a study showing that both pre- and post-menopausal women with breast cancer excreted much lower amounts of phytoestrogens,[30] but a study of Dutch menopausal women showed no significant breast cancer risk reduction in women with a high phytoestrogen excretion.[10] A study of more than 800 Japanese women demonstrated that frequent consumption of miso soup and other isoflavones was associated with a lower risk of breast cancer.[31] A recent review of 18 human studies of a dietary relationship of breast cancer risk to soy protein intake showed no protective effect of the consumption of phytoestrogens with the possible exception of women who consumed phytoestrogens at adolescence or at very high doses.[10] Only four of these studies were prospective and none of them demonstrated a risk reduction.

Adverse Effects of Soy Protein

The consumption of soy protein generally is considered to be beneficial and possibly have protective effects against several common maladies. However, because of the estrogenic activity of these substances, negative effects have been postulated, but there is scant evidence to support this contention.[32] A study to evaluate the pharmakinetics and safety of a purified unconjugated

Suggestions for Adding Soy to the Diet

- Include soy-based beverages, muffins, sausages, yogurt, or cream cheese at breakfast.
- Use soy deli meats, soy nut butter (similar to peanut butter), or soy cheese to make sandwiches.
- Top pizzas with soy cheese, pepperoni, sausages, or "crumbles" (similar to ground beef).
- Grill soy hot dogs, burgers, marinated tempeh, and baked tofu.
- Cube and stir fry tofu or tempeh and add to a salad.
- Pour soymilk on cereal and use it in cooking or to make "smoothies."
- Order soy-based dishes such as spicy bean curd and miso soup at Asian restaurants.
- Eat roasted soy nuts or a soy protein bar for a snack.

Source: U.S. Food and Drug Administration. Adding Soy Protein to the Diet. Available at: http://vm.cfsan.fda.gov/~dms/fdsoypr.html. Accessed Aug. 19, 2003.

isoflavone preparation that delivered single genistein doses of 2, 4, 8, or 16 mg/kg body weight showed minimal toxicity in healthy postmenopausal women, and the pharmacokinetic data suggested that chronic 12-24 hour dosing would not lead to progressive accumulation.[33] An investigational soy isoflavone drug product (PTI G2535) was tested for toxicity and teratogenic effects. Although no toxicity was noted, there remained the concern that isoflavones, specifically genistein, could inhibit topoisomerase and possibly lead to DNA strand breaks. Although there was a statistically significant increase in the frequency of micronucleated polychromatic erythrocytes in the male rats, the increases were small, not dose-related, and spontaneously resolved. In this study, dietary genistein had no negative effects on survival, weight gain, or the incidence or types of tumors that developed in cancer-prone rodents lacking the p53 suppressor gene.[34]

Conclusion

The data at this point, although quite intriguing, do not suggest that any soy protein-specific dietary supplements or dietary changes are helpful in preventing the emergence of breast cancer in adults. The data do suggest that long-term use of soy protein beginning in childhood and continuing through the developmental years into adolescence may be protective against the emergence of breast cancer. There appears, however, to be little harm and perhaps some benefit in pursuing a soy protein-rich diet. ❖

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Alternatives to Menopausal Hormone Therapy

By Sarah L. Berga, MD

ONE OF THE BENEFITS THAT HAS COME FROM THE release of the data from the Prempro® arm of the Women's Health Initiative (WHI) has been a re-evaluation of the pros and cons of menopausal hormonal therapy. In undertaking this appraisal, one inevitably asks what are rational alternatives to hormone use. It is a very logical question. I think we have to accept that many, if not most, women and men want to do what they can to remain as well as possible for as long as possible. Aging gracefully is a worthy pursuit, and we need to find ways to aid those who attempt it. After all, it is a sign of mental health that one wants to minimize age-related disability and disease. However, it is not trivial to outline acceptable alternatives. Consider the following issues.

To delineate alternatives to postmenopausal estrogen or progestin use, one must first understand the benefits and risks of its use. The difficulty inherent in comparing postmenopausal hormone therapy with various alternatives is highlighted by the fact that hormone therapy does not constitute a single therapy. Indeed, although it is not commonly appreciated that each estrogen preparation has unique molecular and tissue effects, the same dose of a given estrogen or progestin does not lead to the same circulating levels in all women or in all tissues within that woman, and not all women stand to benefit equally or suffer the same risks and side effects from postmenopausal estrogen use. Further, progestins differ in their molecular and clinical profiles.

Given this enormous complexity and ever-burgeoning molecular insights, clinicians may feel stymied by a lack of reliable clinical data upon which to guide treatment decisions. Further, the adequacy and acceptability of alternatives to postmenopausal hormone use depend in part on the expectations and goals of therapy. If goals are circumscribed (such as treatment of osteoporosis), then it is easier to delineate several acceptable alternatives. If the goal is to produce in all tissues of relevance an estrogenic effect, but with an absence of estrogen action in tissues in which this effect is deemed deleterious, then that is a much more ambitious undertaking. In asking what might constitute acceptable alternatives to postmenopausal estrogen therapy, one could simply advocate a good lifestyle with an appropriate amount of exercise and an acceptable diet. Or one could advocate a good lifestyle plus periodic surveillance for disorders for which we have good treatment options, such as statins for dyslipidemia. This strategy involves waiting for a disease process to announce itself and then trying to intervene.

The problem is that most health-conscience individuals want to ward off age-related disease and disability before it becomes evident. This means prevention and prophylaxis. The ultimate goal is to retard the aging process. This is also a much more complex task than commonly assumed. While we can enumerate age-related disabilities and diseases, we still don't really understand what aging means at the molecular level. It is hard to imagine how we could reverse or retard a process that is so poorly understood. Fortunately we are making progress in understanding that ontogenic process we call aging. For those aficionados who love science at its best, try reading the Feb. 28, 2003, issue of *Science*, which is devoted to illuminating the many dimensions of aging. In that issue, Juengst and colleagues urge that our scientific institutions must take the lead in ensuring that public discussion of anti-aging research is as deliberate and farsighted as the research itself.[1] If there is one thing we learned from the WHI, it is that strategies advocated for retarding aging hold both promise and peril.

Agents commonly considered as alternatives to postmenopausal estrogen use for preventing age-related disability include selective estrogen receptor modulators (SERMs), phytoestrogens, black cohosh, other herbal agents, and some vitamins. Other "anti-aging" hormones include dehydroepiandrosterone (DHEA), androstenedione (Andro), melatonin, and growth hormone and its analogs. Although acceptance of postmenopausal estrogen therapy has been constrained by recent evidence from the WHI, acceptance of alternatives often is buoyed by hypothetical benefits based on reductionistic assumptions about tissue effects or pathogenetic mechanisms, known benefit in a particular tissue such as bone without demonstrated efficacy in other tissues, and/or lack of long-term data regarding clinical outcomes. Indeed, the more an agent is studied, the more we find out about its risks and side effects. Often, putative benefits do not stand the test of time. The availability of untested or insufficiently tested agents coupled with negative perceptions regarding pharmaceutical estrogens makes counseling menopausal women a challenging task.

CE Objectives

After reading *Alternative Therapies in Women's Health*, the health care professional will be able to:

1. evaluate alternative medicine and complementary therapies for women's health concerns;
2. identify risks and interactions associated with alternative therapies;
3. discuss alternative medicine options with patients; and
4. offer guidance to patients based on the latest science and clinical studies regarding alternative and complementary therapies.

CE/CME Instructions

Physicians and nurses participate in this continuing medical education/continuing education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. After completing this activity, you must complete the evaluation form provided and return it in the reply envelope provided at the end of the semester to receive a certificate of completion. When your evaluation is received, a certificate will be mailed to you.

Despite the limitations of current strategies, our increasing longevity makes it imperative that we continue to search for ways to reduce the burdens of aging. Although we don't quite know why, there can be no doubt that we are on average living longer and longer. Although the field of anti-aging is in its infancy and our initial attempts look as clumsy as the first car or early computers, this line of investigation and intervention is here to stay. Today's task is to help patients understand the gap between expectations and our limited fund of knowledge. It is important for physicians and patients to recognize that we will be forever refining our approaches. Whatever strategies are undertaken will hold both promise and peril, because there is no easy and rapid way to acquire the knowledge needed to hold back the ravages of aging. ❖

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Reference

1. Juengst ET, et al. Aging. Antiaging research and the need for public dialogue *Science* 2003;299:1323.

CE / CME Questions

10. What are the main classes of phytoestrogens found in soy?
a. isoflavones
b. coumestans
c. lignans
d. All of the above

11. Which isoflavones have the most potent phytoestrogenic activity?
a. genistein
b. daidzein
c. biochanin
d. formononetin
e. All of the above

12. Which soy product contains the highest amount of soy protein?
a. Tempeh
b. Soy flour
c. Soy protein isolate
d. Soy sauce

13. Data suggest that long-term use of soy protein beginning in childhood and continuing through the developmental years into adolescence may be protective against the emergence of breast cancer.
a. True
b. False

Answers: 10. d, 11. e, 12. c, 13. a.

Georgetown University Offers CAM Graduate Program

Georgetown University in Washington, DC, is offering a new Complementary and Alternative Medicine (CAM) Masters Program beginning this fall.

The program's designers say it is a scientifically sound program that emphasizes the science of physiology, while offering students a broad insight into CAM and giving them the tools to look critically at its scientific basis. Students will review current research and areas in which more research is needed. The coursework specifically addresses regulatory issues involving CAM modalities and herbal medicine and supplements. Since the program is a "track" within the Masters of Science (MS) program of Georgetown's Department of Physiology and Biophysics, it retains the basic nature of the core curriculum for that MS.

The program planning began a couple of years ago, says Adam Myers, PhD, who is the CAM program director along with Hakima Amrih, PhD. The first graduate class was launched by itself a year ago, and the program directors are expecting about 10 students this year. Eventually they expect the program to hold 20 students.

The Program Mission

Through this three-semester program, Georgetown strives to offer an academically rigorous education in CAM, in the context of traditional basic biomedical sciences. The goal is to train students who will enter into careers in the private and public sector related to CAM research, education, administration, or regulatory affairs. Some of the CAM graduates may apply their CAM training in pursuing further education toward a health care career; others may have been previously trained as practitioners (physicians, nurse practitioners, acupuncturists, nutritionists, pharmacists, etc.), and return to their careers with their additional education.

The program is designed for students who fit into any of several categories in terms of background and eventual career placement:

- students interested in a research career (often with further training at the doctoral level) in a CAM-related area
- students wishing to pursue careers in CAM industry
- students interested in administrative or regulatory affairs careers related to CAM within the public sector
- practitioners or potential practitioners of CAM modalities seeking basic science education relevant to their practices

Students who are interested in the CAM program also need the following to be accepted into the program:

- Bachelor's degree from an accredited university
- completion of prerequisite courses in biology, chemistry, math, and physics
- experience or interest in a CAM-related career
- overall credentials suitable for acceptance to the Graduate School of Arts and Sciences and the graduate programs of the Department of Physiology & Biophysics

A Look at the Curriculum

The CAM graduate program curriculum includes the following topics, presented by faculty of the Georgetown University School of Medicine:

- survey of complementary and alternative medicine;
- fundamentals of biochemistry;
- fundamentals of physiology;
- human nutrition and health;
- mind-body medicine and physiology;
- principles of pharmacology for drugs, supplements, and herbs;
- pathophysiology;
- medical immunology & microbiology;
- critical readings in complementary, alternative, and integrative medicine;
- physiology, biophysics, and CAM seminars;
- statistics and experimental design.

Financial Considerations

Tuition for the Complementary and Alternative Medicine Program is approximately $25,728 (12 credits per semester) for the term. Rates are subject to change.

How To Apply and Contact Information

The CAM program application is online at www.georgetown.edu/departments/physiology/cam/index.html. For information, contact Gina Moses at (202) 687-7979 or gmm27@georgetown.edu.

In Future Issues:

The Atkins Diet

Glucosamine for Osteoporosis