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The Possible Role of Soy in Breast Cancer Prevention and Treatment

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With breast cancer rates continuing to rise in the United States and Europe, researchers have begun to look toward Asia for insights as to why Asian women on the whole have much lower incidence of this devastating disease. Specifically, the age-adjusted death rates due to breast cancer from 1990-1993 were 3.3 times lower for Japanese women than American woman and 4.5 times lower for Chinese women compared to American women (1). Furthermore, there is some experimental evidence that Japanese women who do develop breast cancer have lower rates of metastasis at the time of diagnosis and a much better prognosis than their American and British counterparts (2,3,4). Interestingly, however, it was observed that following immigration from Asia to the U.S., breast cancer rates of immigrants rise over time to eventually parallel those of the Americans (5). Although these observations have yet to be fully explained, the significant difference between Asian and Western diets has been identified as an a likely contributing factor. Within the Asian diet, the high consumption of soy products has been targeted as one possible explanation.

A number of studies have been conducted to examine this hypothesis. In 1991, Lee, et al. compared the diets of 200 Singapore Chinese women with breast cancer to 420 matched controls. They found that for premenopausal women, high intake of soy protein correlated with decreased risk of breast cancer (6). In a 1996 population-based case-control breast cancer study, Wu, et al. studied the diets of Chinese-, Japanese-, and Filipino-American women in Los Angeles, the San Francisco Bay Area, and Oahu, Hawaii. They found that Asian-born Asian-American women consumed more than twice as much tofu as Asian-American women who were born in the U.S. They also observed that, on average, tofu intake decreased for each year that an Asian-born woman lived in the U.S. Finally, they observed a decreasing risk of breast cancer with increasing consumption of tofu in both pre- and postmenopausal women (7). Another recent case-control study investigated the correlation between diet and premenopausal bilateral breast cancer risk. They, too, found an inverse association between tofu consumption and cancer risk. This study is of particular interest because it used sisters as controls in evaluating the relationship of diet to this rare form of cancer with a strong hereditary component. The high familial risk associated with this form of cancer indicates that there is probably a susceptibility gene (such as BRCA1) being passed on from generation to generation. The fact that certain sisters develop cancer while the other sisters do not highlights the important role of environmental factors, such as diet, on cancer risk (8). Despite these numerous studies supporting the hypothesis that soy intake is inversely proportional to cancer risk, the research is not all consistent. A very thorough 1995 study of diet and breast cancer in China did not find any relation between soy consumption and breast cancer risk (9). Because this study appears to have been designed and conducted well, it is not clear why the findings were so different than so much of the other research on this topic. More research of this type should be done to try to determine if the results of this study were merely a "fluke," or if there is some valid explanation for the seeming discrepancy in findings.

If it is true that soybeans provide protection against breast cancer, what is the "active ingredient" within soy that is producing these effects? Ever since the 1930s, it has been known that soybeans contain extremely high amounts of the two isoflavonoids

(isoflavone glycosides) genistein and daidzein. After ingestion, these two diphenol compounds are metabolized by intestinal bacteria into hormone-like compounds. Because of the ability of these metabolic products to bind to and weakly activate estrogen receptors, genistein and daidzein are considered to belong to a group of compounds known as phytoestrogens. However, according to Adlercreutz and Mazur, the estrogenic activity is only a small part of what these isoflavonoids can do in the body. They describe these remarkable compounds as being able to "influence sex-hormone production, metabolism and biological activity, intracellular enzymes, protein synthesis, growth factor action, malignant cell proliferation, differentiation, cell adhesion and angiogenesis in such a way as to make them strong candidates for a role as natural cancer-protective compounds (10)."

If these claims are indeed true, the fact that Westerners on average consume less than 5 mg of isoflavones daily compared with 20-80 mg for Asians could help to explain the great discrepancy in breast cancer rates between the two cultures (11). The remainder of this paper will focus on in vitro and in vivo studies that have attempted to validate and elucidate the hypothesis that the isoflavonoids in soy provide protection against breast cancer.

Animal Studies

In a 1994 review of animal studies related to soy or soybean isoflavonoid diets and experimental carcinogenesis, Messina, et al. reported that 17 out of 26 studies (65%) determined that the soy based diet provided protection against cancer. Of the subset of experiments conducted related to mammary cancer in particular, five out of eight found soy to be protective against cancer and the other three did not see any effect. None of the experiments found that soy increased tumor development. In this evaluation, a treatment was considered to be protective against the cancer if it resulted in an improved tumor number, incidence, metastasis rate, or latency period (12). A separate experiment conducted by Barnes, et al. helps to support the assertion that the isoflavonoids are the specific components of the soy that are responsible for these observed anti-cancer effects. They found that when soy protein concentrate was washed with aqueous alcohol to remove the isoflavones it did not have a protective effect against mammary tumors in the 7,12-dimethyl benz [a]anthracene (DMBA) model of breast cancer. However, when the isoflavonoid-containing aqueous alcohol extract was concentrated to remove the alcohol, the remaining solution did demonstrate a protective effect (13). A recently published study examined the specifics of the timing of the protective properties of genistein in the DMBA rodent model of breast cancer. Specifically, Lamartiniere, et al. demonstrated that rodents treated with genistein as neonates or while prepubescent demonstrated resistance to chemically-induced mammary cancer during adulthood (14).

Mechanisms

As one would expect, a great deal of research has been dedicated to attempting to determine the specific molecular mechanism(s) through which the isoflavonoids exert

these observed anti-cancer effects. Many mechanisms have been proposed, but two of the more explored aspects are hormonal effects and tyrosine kinase inhibition.

In order to begin to understand the role of isoflavonoids in the hormonal aspects of cancer prevention, it is important to appreciate two findings: 1) high levels of circulating estradiol have been linked to increased rates of breast cancer (15) and 2) although genistein has been shown to exhibit weak estrogenic activity, under certain conditions it actually produces powerful anti-estrogenic activity. Although this second finding may seem contradictory, it has been well characterized in animal and in vitro studies (12). Wang, et al. recently demonstrated that low levels of genistein (10^{-8} - 10^{-6} M) stimulated growth on the estrogen receptor positive human breast cancer cell line MCF-7, but higher levels ($>10^{-5}$ M) actually inhibited growth (16).

The human in vivo data is not yet conclusive. A recent study by Nagata, et al. compared soy intake and circulating estradiol levels in 50 healthy premenopausal Japanese women. Although they did demonstrate that intake of soy products was inversely proportional to circulating estradiol levels, they were unable to provide a complete explanation for their findings. They postulated that these observations may be due to the effects of isoflavones and their metabolites on intestinal steroid hormone metabolism, which in turn affects estradiol concentrations (17). Older research by Adlercreutz found that isoflavonoids cause the synthesis of sex hormone-binding globulin (SHBG) in the liver. Because increased levels of SHBG would reduce the biological effects of sex hormones, they believed that this could be the link between high levels of genistein and low levels of hormone-dependent cancer (18,19). However, in their study, the Nagata team did not observe any significant correlation between soy intake and SHBG levels (17). As can be seen from this apparently conflicting data, much still needs to be learned before the mechanisms of the estrogen/antiestrogen effects are fully understood.

Another, potentially related, proposed anti-cancer mechanism of genistein is its inhibition of tyrosine kinase. In 1987, Akiyama, et al. demonstrated in vitro that genistein can act as a potent tyrosine kinase inhibitor by competitively inhibiting ATP binding to the catalytic domain of the enzyme. They demonstrated that genistein-induced inhibition of tyrosine kinase activity occurs in growth factor receptors (EGF, PDGF, insulin, and IGF) and certain oncogene products (20). Despite these seemingly promising findings, researchers have been having difficulty directly observing protein kinase inhibition in relation to breast cancer inhibition. A 1996 study by Peterson and Barnes attempted to link the protein tyrosine kinase inhibition with the anti-growth effects of genistein on human breast cancer cell lines. Despite observations that genistein effectively inhibited growth of five separate human breast cancer cell lines, they could not identify any specific evidence of gross protein tyrosine kinase inhibition. They did observe that the mechanism of growth inhibition occurred equally well in estrogen-receptor positive and negative cell lines, indicating that the growth inhibition is not dependent on the presence of a functional estrogen signaling pathway. However, they could not pinpoint the specifics of what factors were actually responsible for the growth inhibition (21). In a slightly different experiment, Ablner, et al. arrived at similar findings. In their study, they explored the effect of genistein on insulin receptor tyrosine kinase activity and metabolic effects of

insulin in isolated rat adiposites. Based on the understanding that genistein is a potent tyrosine kinase inhibitor, they hypothesized that they would observe tyrosine kinase inhibition as the method of blocking certain intracellular insulin responses. However, what they found instead was genistein-induced inhibition of certain insulin responses without evidence of interference with either the receptor tyrosine autophosphorylation or receptor kinase substrate tyrosine phosphorylation (22). Due to the plethora of unanswered questions regarding the exact biochemical mechanisms involved in genistein-induced anti-cancer activity, this will undoubtedly remain an extremely active area of research.

Conclusion

Despite the presence of conflicting and sometimes confusing findings, there is a significant body of evidence that supports the hypothesis that high consumption of soy can lower breast cancer risk. Given this, it seems plausible to begin to explore the concept of soy "chemoprevention" to reduce the risk of and mortality from breast cancer. At a minimum, American women could consciously begin to incorporate increased amounts of tofu and other soy products into their diets. Because we do not yet have enough information about either the recommended dosage or possible toxicity of purified or synthetic genistein, it makes sense to consume genistein in its natural "soy food" state. Having been eaten in large quantities by Asians for centuries, tofu and other soy products have already demonstrated their long-term safety. Two other key advantages to using soy protein in its natural form are that 1) when eaten in its "whole food" form, soy provides a multitude of other nutrients and fiber, and 2) it is available for one-eighth the price of purified genistein. It also follows that this is an appropriate time to initiate prospective clinical trials with soy to further assess its potential effectiveness at preventing, arresting, and reversing breast cancer in humans. Barnes and his colleagues report already having begun such studies (23).

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