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On The COVER

Fighting Cancer Naturally

By John F. Lauerman

Over the past five years, the anti-cancer effects of soy protein have been extensively studied.

Wouldn't it be great if you could open a bottle marked "Cancer Prevention Agent," knowing that what was inside would drastically reduce the likelihood of your developing this dreaded disease?

Perhaps you can, if the new evidence about phytoestrogens in soy protein is any indication. Phytoestrogens, or plant estrogens, are found in high quantities within soybeans and soy foods, such as soy flour, soy milk and tofu. Eastern cultures where large amounts of soy products are consumed, such as China and Japan, boast significantly lower rates of breast and prostate cancer.

"In the last five years, a database has emerged showing that consuming nutrients in amounts greater than that which can be consumed in foods may have [cancer] benefits," says Mark Messina, Ph.D., a consultant and former National Institutes of Health researcher who organized the first and second International Symposia on The Role of Soy in Preventing And Treating Chronic Disease.

"This has been indicated in vitamins, fish oils and other dietary components," says Messina. "It may not be possible to meet effective levels without consuming fortified foods, so there's a shift to a demand for supplements. In the case of genistein, there's some data suggesting that the amount you may need to derive certain desired benefits may be higher than that which can be consumed in a normal soy-containing diet."

Although many researchers continue to be excited about genistein's potential, there are the inevitabl calls for additional research. caution. Steven Clinton, M.D., Ph.D., a researcher at the Dana Farber Cancer Institute in Boston, is currently studying chemoprevention of bladder and prostate cancer. While he's hopeful that genistein may yet provide some assistance in preventing or treating cancer, Clinton advises that caution is needed before mega-doses of genistein are considered appropriate.

Supporting studies are coming quickly, however. Researchers looking for a specific phytoestrogen responsible for cancer prevention have focused their attention on genistein, an isoflavone phytoestrogen found almost exclusively in soybeans. In studies of brain, prostate, liver, skin, stomach, bladder and breast cancer, genistein has shown intriguing possibilities for prevention and perhaps even treatment of cancer. Researchers also are optimistic that this compound may prove of some use in prevention of osteoporosis and heart disease.

There appears to be cultural evidence to support these theories. A 1980 research review by British epidemiologists Sir Richard Doll and Richard Peto showed distinct variations in the incidence of various types of human cancer from country to country. For instance, stomach cancer is most prevalent in Japan, while cancers of the colon, breast and lung predominate in the United States.

When these observations were first made, no one knew whether genetics or environment was responsible for such variations in cancer incidence and mortality. However, when researchers followed people from one culture to another, it appeared that the changing dietary patterns of individuals moving from one country to another would alter the appearance of their cancer risk profiles. For instance, Chinese people who emigrated to the United States and maintained their traditional diets, developed cancer in the same epidemiological patterns as they had in their home countries. Disease patterns among those who became culturally "assimilated" and began eating Western diets, however, became less like those seen in their home countries and more like those typically found in the United States.

It became clear that diet is a major variable in different cultural environments. The observation between diet and cancer risk has

sparked vigorous investigation into the anti-cancer nature of certain foods, particularly vegetables and legumes, which in certain clinical and animal experiments have demonstrated some curative and preventive properties. Numerous studies have documented lower incidences of cancers of the breast, colon, ovary, prostate and other organs in cultures where low-fat, high-fiber diets are consumed regularly.

Genistein has a number of very interesting properties which may be responsible for an anti-cancer effect. Genistein's molecular structure resembles that of estrogen, a sex hormone with powerful effects on the growth, differentiation and function of many cells. Researchers believe that genistein's hormonal action might prevent cancer in a number of organs. And, a 1997 study from the Karolinska Institute showed that the distribution of estrogen receptors throughout the human body is wider and more concentrated in some tissues than previously believed, adding credence to the theory that manipulating estrogen-binding might have broad effects in cancer prevention.

Some animals are very sensitive to these estrogens; in fact, plant estrogens were first discovered after Australian farmers found that sheep grazing on red clover-clover that turned out to be high in phytoestrogens-were rendered infertile. Researchers suspect that zoo-confined cheetahs also have been rendered infertile in the same way after they were fed soy products.

In humans, however, genistein is a "weak estrogen," meaning that its hormonal effects are not as strong as those of estrogens normally produced by the human body. Adding a weak estrogen like genistein to the diet does not necessarily raise the level of estrogenic activity in the body. On the contrary, genistein appears to compete with stronger estrogens for estrogen receptor sites. This means that genistein can block the activity of stronger estrogens, thus reducing overall hormonal activity.

Over the last few years, several researchers in the U.S. and in Europe proposed that genistein might inhibit the growth of hormonally induced tumors by blocking estrogen activity, much like the action of tamoxifen, another estrogen inhibitor. Consequently, researchers considered genistein a candidate to prevent or control tumors in which hormones play an important role, such as breast and prostate cancer.

Mindy Kurzer, Ph.D., associate professor of nutrition at the University of Minnesota in St. Paul, who has looked at genistein in cell culture, says its hormonal effects are still difficult to pinpoint.

"When we're just looking at cells, we found that there's a biphasic effect," she says, meaning that at low concentrations isoflavonoids stimulate cell growth, but at high concentrations-much higher than you would normally expect to find in the bloodstream of a person eating soy-they inhibit growth. "This goes against the common thinking that we've seen and heard about dietary amounts of phytoestrogens inhibiting estrogen, so we're more inclined to think that there may be multiple mechanisms for genistein to affect cell growth."

Recently, Steven Barnes, Ph.D., associate professor of toxicology and pharmacology at the University of Alabama-Birmingham, observed that genistein stopped growth in cells that had no way to bind estrogen. This led him to look into another possible mechanism of action that several labs have found productive-genistein's effects on "cell signaling," the messages cells get determining when to mature into the different kinds of cells the body needs in order to function. Consequently, he also has stepped away from looking at genistein as functioning through its effect on estrogen binding, and has started looking at other mechanisms through which genistein may prevent cancer.

Cells that fail to mature, or differentiate, frequently become cancer cells, and it appears that faulty signaling within the cell may play that role in some cancers. An important cell-signaling molecule is tyrosine kinase that, when activated (phosphorylated) by enzymes, turns on growth factors and related substances.

"Isoflavones like genistein appear to behave like tyrosine kinase," says Barnes, "which we know to be particularly important in abnormal processes, especially cancer. In some cases, it looks as if genistein is so similar to tyrosine kinase that it gets in the way of phosphorylation, and thus slows down these growth-factor responses and their activity."

In a 1997 study from the University of Vermont Cancer Center, researchers used genistein to block protein tyrosine kinase in cultured rat brain-tumor cells. These cells, called glioblastomas, are found in a very aggressive, lethal form of brain cancer that is often associated with brief patient survival. In the study, genistein appeared to block the activation of the epidermal growth factor receptor, which has been consistently linked with tumor growth and patient prognosis. The study's authors concluded that only relatively low concentrations of genistein could block glioblastoma's invasion of brain tissue, an important step in metastasis, the process by which cancer spreads throughout the body.

In addition, some studies of genistein have shown that it appears to stimulate cancer cells to mature and differentiate. This is important because, while normal cells go through a process of maturation and differentiation into the various cell types that perform work for our body, most cancer cells appear to be stuck in their maturational cycle. Such cancer cells often are called "immortal" because they do not die, as normal cells do; however, in some cases genistein has stimulated such cancer cells to die.

Another study linking genistein's inhibition of protein tyrosine kinase to cancer treatment and prevention was published in 1996 by researchers at the University of Edinburgh Medical School, in Scotland. When genistein and another inhibitor, tyrphostin-25, were used to block the activation of protein tyrosine kinase, cultured small-cell lung-cancer cells matured and died a "natural" death of apoptosis. The cells were, in effect, "de-immortalized."

Like most cells, cancer cells need blood, and large, metastatic tumors secrete substances that stimulate the formation of blood vessels whose purpose is to feed the tumor. A number of biotechnology firms are looking at various compounds that block the new formation of blood vessels, a process also called angiogenesis that would thus be able to choke off the supply of oxygen to growing tumors.

Diets that are rich in vegetables and soy have been associated with the prevention of new blood vessel growth and its resulting diseases. In one European study conducted in 1993, researchers broke down the urine of people consuming a diet rich in soy, attempting to isolate compounds that would block angiogenesis. The most potent growth-blockers contained concentrations of genistein. Later, a study from Johns Hopkins University School of Medicine, in Baltimore, Md., showed that, by blocking the protein tyrosine kinase pathway, genistein prevented the growth of blood vessel cells in culture.

Several studies have related soy intake to reduced colon cancer. In fact, higher rates of colon cancer among soy consumers were observed only when soy was eaten as a fried food. In countries with high consumption of dietary soy, there is a twofold reduction in deaths from colon cancer, compared with the United States.

All of this constitutes a mounting body of evidence that is increasingly compelling.

When asked about the cancer prevention potential of soy, the Dana Farber Cancer Institute's researcher Steven Clinton says, "We have firmer ground to stand upon with soy foods than any chemical."

The Life Extension Foundation does not recommend that women with estrogen-receptor positive breast cancer use soy genistein, based on evidence that an estrogenic growth effect could occur in some forms of estrogen-receptor positive breast cancer. Until more is known about the effects of soy phytoestrogens in this type of cancer, compounds such as genistein should be avoided in those with estrogen-receptor dependent breast cancer.

One study tested the effects of naturally occurring flavonoids on the proliferation of an estrogen receptor-positive human breast cancer cell line. Genistein inhibited cell proliferation, but this effect was reversed when estrogen was added. The flavonoids hesperidin, naringenin and quercetin inhibited breast cancer cell proliferation, even in the presence of high levels of estrogen. These flavonoids apparently exert their anti-proliferative activity via a mechanism that is different from genistein.

Women with any type of breast cancer should test their serum estrogen levels to make sure that too much estrogen is not present if they are taking high doses of soy. Estrogen can combine with the phytoestrogen genistein to cause some breast cancer cells to grow faster. Other studies show that genistein blocks certain types of estrogen-receptor sites, thus inhibiting the proliferation of these types of breast cancer cells.

Most cancer patients whose tumors have a mutated form of the p53 oncogene are far more likely to benefit from soy extract supplementation. But in small cell lung cancer it was determined that genistein's growth-inhibitory effects were independent of p53 function. Only a pathology examination of the actual cancer cell can determine p53 status. An immuno-histochemistry test canhelp determine the p53 status of tumor cells.

If the test is positive, you have mutant p53 and are more likely to benefit from soy extracts. If the test is negative, this indicates that you have functional p53 and are less likely to benefit from soy extracts.

The Foundation realizes that many cancer patients seeking to use soy supplements may find it difficult to have an immuno-histochemistry test performed to ascertain p53 status. The Foundation is working on a blood test that would reveal p53 status, and thus enable the cancer patient to determine whether high-potency genistein supplementation might be helpful.

Since all cancer therapies produce individual responses, the Foundation again recommends that cancer patients have monthly blood tumor marker tests to determine if therapies are working or not. If, say, tumor markers were to continue to elevate 30 to 60 days after initiating soy extract supplementation, discontinue its use and seek another therapy immediately.

Some cancers do not have blood marker tests. In these cases, MRI, CAT scans or other imaging techniques should be used to determine whether or not tumor shrinkage is occurring. If 30 to 60 days of supplementation with 20 700-mg capsules a day of Mega Soy Extract does not cause tumor shrinkage, then consider other therapies.

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