

LE Magazine October 1999

REPORT

I3C, Indole 3 carbinol
The Tamoxifen Substitute
Cancer Prevention For Thinking People

The FDA's recent approval of tamoxifen for the reduction of the risk of breast cancer in high-risk healthy women prompted us to take a closer look at the drug. What we discovered may surprise you. Tamoxifen works by blocking estrogen, but blocking estrogen is not its only, or in some cases, most important action. The anti-cancer effects of tamoxifen are found in other substances that are far less toxic and just as powerful. Stay with us-what you learn may save your life.

Estrogen and breast cancer

Genuine human estrogen is a hormone with important functions in multiple areas of the body. Essentially a chemical messenger, estrogen interacts with cells as diverse as skin, gut, breast and brain.

Estrogen sends messages to cells through what are known as estrogen receptors. Receptors are essentially "doors" on cells that allow entry of substances like estrogen. In the case of estrogen, the "door" is very big, and it will also allow molecules that resemble estrogen to enter as well. This is why fake estrogens and estrogen blockers can provoke cells to react. If the receptor was very small or very particular, it wouldn't allow the fakes in.

Receptors are not like doors, however, in the sense that they're not square. They're curvy-like a jigsaw puzzle. When a molecule of the right shape comes along, it fits in the receptor and makes contact with points just inside the receptor's "door jamb." Touching these contact points sets off a series of chemical reactions that send a signal inside the cell.

One of the most important messages estrogen delivers is to grow-divide, multiply. For this reason, estrogen is crucial in the development of the fetus. For the same reason, it's usually found at the scene of breast cancer, where it eggs on hormone-responsive cancer cells. It's estimated that 50-70% of all breast cancers are estrogen receptor-positive-they grow in the presence of estrogen. And according to Dr. Kent Osborne of Baylor University, this figure could be much higher because of problems in the classification system.

Successful communication between the messenger and the cell depends on the messenger (estrogen) fitting the door (receptor) exactly so as to make all the contact points. Estrogen produced naturally in the body fits inside the estrogen receptor perfectly and sends certain predetermined signals. Estrogen look-alikes such as tamoxifen fit in the door, but don't make all the contacts because they're not exactly the right shape. As a result, they send odd signals or block them altogether.

What's disturbing about these synthetic look-alikes is that scientists don't know what signals they actually do send once they get into the receptor. They know some of the signals. For example, they know that tamoxifen blocks the "grow" signal in breast tissue. They know the same molecule promotes the "grow" signal in uterine tissue. They know Premarin sends a "grow" signal to bone. But what signals, for example, does the estrogen mimicker/blocker, raloxifene, send to the brain through its estrogen receptors? Nobody knows.

Secrets of tamoxifen

The most well-publicized aspect of tamoxifen's mode of action against breast cancer is that it blocks estrogen. What's not usually appreciated is that tamoxifen has other modes of action. The other actions are just as important, or in some cases more important, than the estrogen-blocking effect. And they are not unique to tamoxifen.

Tamoxifen also works in estrogen receptor-negative breast cancers and progesterone receptor-positive breast cancers. This is because tamoxifen not only blocks the estrogen "grow" signal, it blocks another type of "grow" signal known as protein kinase C (PKC). PKC is another one of those contact points inside the door jamb, and blocking this signal stops oncogenes (cancer genes) from activating. PKC also controls cell growth and transformation signals.



Tamoxifen promotes free radicals

A surprising study was published in the *Journal of Biological Chemistry* in 1996. Using estrogen receptor-negative breast cancer cells, researchers from the University of Southern California showed that tamoxifen uses free radicals to inhibit PKC. How it generates the radicals is not known. Researchers do know, however, that it takes very low doses of tamoxifen to create this effect. Estrogen receptor-positive cancer cells require much higher doses of tamoxifen. A very important finding of this study is that antioxidant vitamins E, C and beta-carotene (but not glutathione) kept tamoxifen from working in estrogen receptor-negative cells. If confirmed in vivo, this could mean that women with receptor-negative breast cancer taking tamoxifen should not take antioxidants.

A group at Zeneca Pharmaceuticals, the manufacturer of tamoxifen, has reported a similar phenomenon. In estrogen receptor-negative ovarian and leukemia cells, tamoxifen depletes the body's natural antioxidants and provokes free radicals. The radicals then cause the cancer cells to self-destruct. An important caveat of both this and the above study is that both have only been done in the test tube and only in estrogen receptor-negative cancer cells.

Tamoxifen also stops free radicals

It's not surprising that tamoxifen generates free radicals since most, if not all, chemotherapies do. However, it is surprising that tamoxifen is also a powerful antioxidant. The antioxidant effect is found in its metabolite, 4-hydroxytamoxifen.

Women who take tamoxifen for 6 months have far fewer free radicals in their blood than before they took it. They also have higher levels of antioxidant vitamins and enzymes, indicating that tamoxifen conserves the body's own antioxidant defenses (except in the above studies in estrogen receptor-negative cells).

Numerous studies show that 4-hydroxytamoxifen strongly inhibits oxidative damage to a broad range of important substances-lipids, DNA and protein. This ability to stop free radicals is part of its anti-cancer effect. In studies on animals treated with the chemical TPA, tamoxifen was effective at inhibiting free radicals so that not enough DNA damage occurred to transform the cells.

Another aspect of tamoxifen's anti-cancer action is its ability to interfere with the cell cycle. The cell cycle is a predetermined program a cell goes through to make a new cell. Normal cells "put on the brakes" at certain points during the process so that things can be checked for accuracy. This ensures that abnormal cells don't get duplicated. However, cancer cells "override" the brakes. They duplicate themselves at break-neck speed with no checks on accuracy. Chemotherapy works by "setting" the brakes. Tamoxifen is one of the chemotherapies that does this.

What's wrong with tamoxifen

All this sounds great. Why not take tamoxifen and be happy? Because tamoxifen has severe drawbacks, some of which are just now coming to light. While some studies show that tamoxifen works better at five years than two, other research confirms that tamoxifen always "turns" on its user in months or years, and begins feeding new, tamoxifen-dependent cancer. A new chemical is being tested to combat this "problem." But the new chemical may create problems of its own.

Meanwhile, there are hints that tamoxifen "resistance," as it's known, is the result of permanent damage caused by the drug. One area that might be damaged is tumor suppressor gene p53, a player in the process that stops the cell cycle and makes sure cancer cells don't get replicated. In the healthy person, p53 sends signals that stop the cell cycle when abnormal cells are involved, and causes them to self-destruct. Using human breast cancer cells, researchers in France showed that tamoxifen stops p53 from working. While this may sensitize cancer cells to the effects of chemotherapy, the same phenomenon in a healthy person would cripple their ability to stop cancer.

The National Cancer Institute and Sloan Kettering Cancer Center have both reported that tamoxifen causes mutations in endometrial cells, including mutations in p53. More than one group has called for more research in this area, but it hasn't been done.

There is evidence that tamoxifen causes another problem which hasn't been adequately investigated. Constant exposure to the drug may permanently alter the estrogen receptor. Receptors have "plasticity"-their shape can change depending on what "fits in the door jamb." Tamoxifen doesn't fit into the estrogen receptor just right. As a result, the estrogen receptor changes its shape to fit tamoxifen. The same phenomenon happens in people who chronically take mood-altering drugs. Their neurons adapt to the drug. This is part of the phenomenon of drug tolerance and withdrawal-the receptors have adapted to the artificial drug and depend on it to function. No one knows whether tamoxifen permanently damages the estrogen receptor in the same way.

These unknowns, coupled with the elevated risk of life-threatening blood clots and uterine cancer, the lack of evidence that tamoxifen prevents breast cancer at all in healthy women, plus the lack of an accurate risk assessment tool of who is really at risk (see "Tamoxifen: Cancer-causing Drug Approved for Healthy Women," Life Extension magazine, May 1999), make tamoxifen risky

as a cancer prevention strategy.

Indole-3-Carbinol: The thinking person's cancer prevention

Tamoxifen is a chemical proven to provide short-term delay in the reemergence of breast cancer in women who have already had breast cancer. There is no evidence that it prevents breast cancer in women who have never had it. There is evidence, however, that tamoxifen stops working within months and starts feeding new, tamoxifen-dependent tumors, and causes an elevated risk of uterine cancer and blood clots.

Despite these drawbacks, however, the drug possesses some very desirable characteristics. It has powerful antioxidant action, plus the ability to inhibit PKC. Its ability to block estrogen's "grow signal," and stop cancer cells from growing are very important characteristics. Yet who wants to take a drug that can potentially cause cancer and a host of other ills? Is there anything better?

In 1991 researchers at the Institute for Hormone Research in New York City announced that they had been able to induce the body to convert the stronger form of estrogen (estradiol) into a weaker form (2-hydroxy-estrone) without using drugs. 2OHE is considered to be a more desirable form of estrogen. It is less active than estradiol, so when it occupies the estrogen receptor, it effectively blocks estradiol's strong "grow" signals.

Natural substance changes the way estrogen is metabolized

It took only one week to prove that the conversion of estradiol to 2OHE can be accomplished without drugs. Using a natural substance, researchers were able to increase the conversion of estradiol to weak estrogen by 50% in twelve healthy people.

Next, they tested the natural substance in female mice prone to developing breast cancer. Both the incidence of cancer and the number of tumors fell significantly. What was the substance? Indole-3-carbinol (IC3), a phytochemical isolated from cruciferous vegetables (broccoli, cauliflower, Brussels sprouts, turnips, kale, green cabbage, mustard seed, etc.).

IC3 was then given to 25 women for two months. Again, levels of strong estrogen declined, and levels of weak estrogen increased. But more importantly, the level of an estrogen metabolite associated with breast and endometrial cancer (16alpha-hydroxyestrone) fell.

Product Information

INDOLE 3 CARBINOL

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I3C Indole 3 carbinol The Tamoxifen Substitute Cancer Prevention For Thinking People.

And more. . .

In 1997, researchers at Strang Cancer Research Laboratory at Rockefeller University discovered that when I3C changes "strong" estrogen to "weak," it stops human cancer cells from growing (54-61%) and provokes the cells to self-destruct (apoptosis). Subsequent studies done at the University of California at Berkeley, show that I3C inhibits MCF7 human breast cancer cells from growing by as much as 90% in culture. Growth arrest does not depend on estrogen receptors.

I3C does more than just turn strong estrogen to weak. 16alpha-hydroxyestrone (16OHE) is an estrogen metabolite that is biologically active-i.e., like estradiol, it can send "grow" signals. In breast cancer, the bad 16OHE is elevated, and the good 2OHE is decreased. Cancer-causing chemicals change the metabolism of estrogen so that 16OHE is elevated. I3C changes them back so that 2OHE is increased.

In an experiment at New York University, researchers gave African-American women I3C, 400 mg for five days. Most of them experienced an increase in the "good" 2OHE and a decrease of the "bad" 16OHE. However, some did not. It turns out that those who did not have a mutation in a gene that helps metabolize estrogen to the 2OHE version. Those women have an eight times higher risk of breast cancer.

The I3C receptor

A startling discovery shows that I3C controls estrogen metabolism through the same receptor that allows dioxin into the cell-the "Ah" receptor (aryl hydrocarbon). Ah is similar to the estrogen receptor in that it can induce cellular growth. Unlike the estrogen receptor, however, scientists haven't found the body's natural "Ah" that fits into the Ah receptor. The only substances known to activate Ah are certain phytochemicals, including I3C-and the proven cancer promoter, dioxin. Dioxin is a chemical made from chlorine. It's so toxic that scientists measure it in trillionths of a gram. It's used in all kinds of things-from Saran Wrap(r) to pesticides to wood preservative. It has been detected in McDonald's Big Macs(r), Haagen-Daz(r) ice cream and Kentucky Fried Chicken(r). Meat, dairy products and fish are the most concentrated sources. When paper is bleached or plastic is burned, dioxin is released into the environment. Because it lodges in fat, it's almost impossible to remove from the human body. Losing weight simply causes it to hunker down in the remaining fat.

A study on people who worked in a dioxin plant shows that women exposed to the chemical have more than twice the risk of breast cancer, but some studies don't show any association at all. Part of the problem with dioxin studies is that there are hundreds of similar chemicals, with hundreds of different metabolites that may interact in ways we don't currently understand.

Dioxin, like I3C, affects estrogen metabolism. For this reason, it has been called an estrogen blocker (like tamoxifen). But it doesn't work through the estrogen receptor. Dioxin and I3C both affect estrogen metabolism through the Ah receptor. But just as tamoxifen sends a different signal than genuine estrogen when it gets in the estrogen receptor, so does dioxin send a different signal than I3C in the Ah receptor. In addition to changing the metabolism of estrogen, dioxin also disrupts other important growth regulatory factors. Among those factors are insulin, IGF-1 (insulin-like growth factor), and tumor necrosis factor (TNF). It also activates cancer genes and suppresses tumor suppressor genes.

I3C, on the other hand, fits into the Ah receptor, but instead of sending signals that help cancer grow, it sends signals that stop it. I3C uses the Ah receptor to indirectly affect estrogen metabolism also, but in a beneficial way. Not only does it positively affect estrogen, it can also keep dioxin out of cells. When researchers at Texas A & M University treated breast cancer cells with I3C and dioxin at the same time, dioxin's adverse effects were reduced 90% by I3C.

I3C prevents chemically-induced breast cancer in rodents by 70-96%. It also prevents other types of cancer, including aflatoxin-induced liver cancer, leukemia and colon cancer. Studies show that I3C inhibits free radicals, particularly those that cause the oxidation of fat.

I3C stops cancer cells from growing

I3C not only weakens estrogen and keeps chemicals out of cells, it also goes after cancer in ways similar to tamoxifen. It, like tamoxifen, interrupts the cell cycle. In studies from the University of California mentioned above, I3C inhibited the growth of estrogen receptor-positive breast cancer cells by 90% compared to tamoxifen's 60% by stopping the cell cycle. (Adding tamoxifen to I3C gave a 5% boost.) In estrogen receptor-negative cells I3C stopped the synthesis of DNA for new cells by about 50% whereas tamoxifen had no significant effect. I3C also restores p21 and other tumor suppressors that act as check points during synthesis of a new cell. Tamoxifen, by contrast, has no effect on p21. I3C also inhibits cancers caused by other chemicals, in addition to dioxin. If animals are fed I3C before exposure to certain other cancer-causing chemicals, DNA damage and cancer will be virtually eliminated. A study on rodents shows that damaged DNA in breast cells is reduced 91% by I3C. Similar results happen in the liver. And in a study from New York University Medical Center, female smokers taking 400 mg of I3C significantly reduced their levels of a major lung carcinogen. Chemicals in cigarettes are known to affect estrogen metabolism.

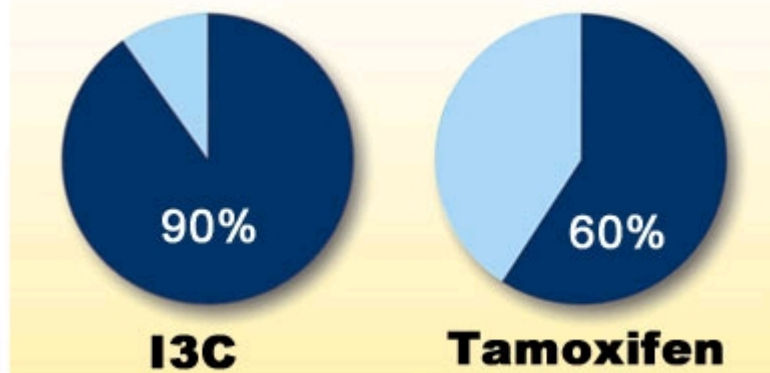
While there is no proven breast cancer preventive, the best and most comprehensive scientific evidence so far stands behind phytochemicals such as I3C. I3C beat out more than 80 other substances, including tamoxifen, for anti-cancer potential in an assay done at the National Cancer Institute.

Recently, researchers at the Hoechst Marrion Roussel drug company staked patent claims to dozens of indole-3 look-alikes. They claim that the indoles, which down-regulate estrogen receptors, can be used to treat and prevent cancer and autoimmune diseases such as multiple sclerosis, arthritis and lupus. They hope to replace all the chemically-altered estrogen drugs such as tamoxifen with a new generation of chemically-altered indole drugs that fit in the Ah receptor, and regulate estrogen indirectly. Will the fake indoles create cancer in other organs as tamoxifen does? Will they lead to chemical tumor dependency as tamoxifen does?

Time will tell if the constant stream of chemical lookalikes will continue to stop/feed cancer. In the meantime, those wishing to get off the chemical merry-go-round, and get serious cancer prevention without the side effects have a terrific option: I3C.

Inhibition of growth in estrogen

receptor-positive breast cancer cells



Note: we cannot say that I3C will absolutely prevent breast cancer. The studies that would allow us to give you the absolute proof haven't been done.

Currently there are two government-sponsored trials underway involving estrogen metabolism and vegetables. One is going to assess the "interactive effects of dietary fat and fruits and vegetables on the levels of oxidative DNA damage and cholesterol oxides in women at high risk for breast cancer." This study is enrolling a grand total of 160 women in the next two and a half years. The other plans to look at how fiber affects estrogen metabolism in postmenopausal women. This study is enrolling a phenomenal 40 women over four years. Should the government ever get serious about preventing breast cancer, and spend \$100 million of your tax dollars on testing I3C as they have on testing tamoxifen, we would be able to give you the proof. For now, we can only give you the best evidence and let you decide.

Recommended Dosage/Precautions:

Note that while a little is good, a lot is not necessarily better. As with certain antioxidants that can actually promote oxidation at high levels, too much I3C can have the opposite effect of what you want. Therefore, don't exceed the dosage. The effective dose established in human studies is 6-7 mg per kg of weight per day. For a 120 lb. woman, this is just under 400 mg/day.

Also note that pregnant women should not take I3C, due to its modulation of estrogen. The reported aversion to cruciferous vegetables by pregnant women may be associated with their ability to change estrogen metabolism.

Product Information

INDOLE 3 CARBINOL

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