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On The COVER

TAMOXIFEN

Cancer
Causing
Drug Approved
For Healthy
Women

Despite what you might have heard, the use of tamoxifen for breast cancer prevention is highly controversial. The drug has not been proven to prevent breast cancer. And while its long-term effects on healthy women are unknown, tamoxifen's cancer causing properties are well documented.

In a stunning move, the Food and Drug Administration approved the use of tamoxifen (Nolvadex) chemotherapy for healthy women with no evidence of breast cancer. The approval came after almost two decades of wrangling over research that cost American taxpayers hundreds of millions of dollars, created fraud, prompted a congressional hearing, and spanned great controversy. The FDA's decision—announced on October 30, 1998—allows Zeneca Pharmaceuticals to tap into a market potentially worth 36 billion dollars annually. The decision allowing the drug to be sold for breast cancer prevention was made despite objections from women's health organizations and researchers around the world. When the advisory committee recommending approval was asked whether the tamoxifen prevention study demonstrated that the drug had "a favorable benefit-risk ratio for the prevention of breast cancer in women at increased risk as defined by the study population," it said "no" unanimously. Yet, the FDA approved tamoxifen for healthy women anyway.

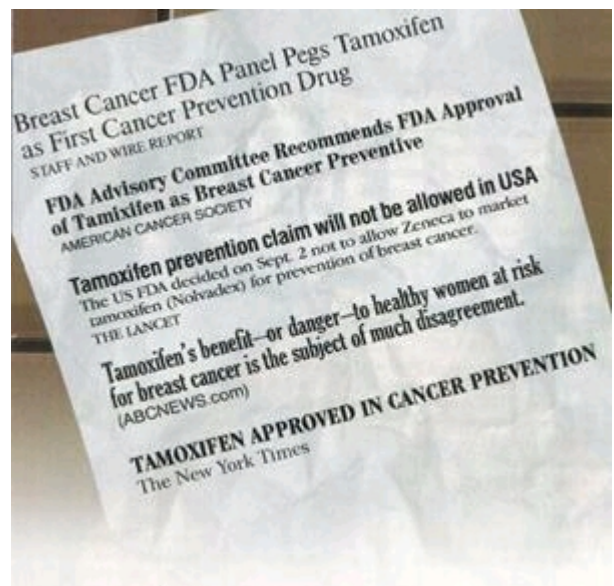
Tamoxifen is a synthetic estrogen blocker—one of many that have been around since the early '70s that once had potential as birth control pills. Like diethylstilbestrol (DES) tamoxifen blocks estradiol, but also like DES, it has estrogenic properties that cause cells to grow. Despite its dual personality, tamoxifen has been successfully used to prevent recurrence of breast cancer in women who are estrogen-receptor positive.

Using tamoxifen in cancer patients is one thing; using it in healthy women is another. Tamoxifen is a well-known carcinogen which causes DNA strand breaks. This is an accepted feature of standard chemotherapy where the overriding concern is to keep cancer cells from growing. Carcinogens have not traditionally been an accepted part of preventive medicine, however. The FDA's decisions to allow the sale of tamoxifen and certain cholesterol-lowering drugs (notably the peroxisome inhibitors clofibrate and gemfibrozil) to healthy people marks the first time that drugs with cancer-causing potential have been approved as health enhancements. We believe this marks a dangerous new trend in drug approval.

The paucity of data makes the approval of tamoxifen for prevention particularly questionable. Approval was based on a single study run at various hospitals around the United States under the auspices of the National Cancer Institute (NCI). An outgrowth of the "National Surgical Adjuvant Breast and Bowel Project" (NSABP) begun in the '80s, the study was about 10 years shy of producing any meaningful information, according to one expert. Two similar European studies reported no preventive effect of tamoxifen. The FDA rejected these studies as irrelevant because they were too small (3500 people combined).

The Hype

There was no statistical difference in survival for the women taking tamoxifen versus women taking placebo in the NCI study. The justification for Zeneca's claim of a 50% reduction in breast cancer lies in the difference between a 1.4% incidence of cancer in women taking tamoxifen versus a 2.7% incidence in those taking placebo. The price of that 1.3% difference was very dear. Tamoxifen doubled the risk of endometrial cancer for women under 50. It quadrupled it in women over 50.



In short, what a healthy woman over 50 got when she took tamoxifen was a proven four times higher risk of endometrial cancer in return for an unknown amount of risk reduction for breast cancer in the short term. And that's not all. Thirty-five tamoxifen-takers developed blood clots in the lung, and three of them died. The risk of cataracts was doubled, and almost half the women participating rated the side effects as "quite a bit or extremely bothersome." Technically, tamoxifen also doubled the risk of suicide (two on tamoxifen versus one on placebo). Worth it? Well, there was a 0.4% reduced risk of a certain type of bone fracture.

"Women of color" got a more definite picture of what tamoxifen could do for them. Their risk of breast cancer was doubled. However, this wasn't played up in the media because too few "women of color" were enrolled in the study to make the statistics significant. The eighteen-page report of the study published in the *Journal of the National Cancer Institute* glanced over the issue in three sentences, and even making the numbers sound promising.

Other Studies Find No Benefit

Two European studies reported interim findings about the same time as the NCI study, which wrapped up early. Both found no preventive effect of tamoxifen in healthy women. The authors of the NCI study devoted considerable space to discrediting these two European trials. One of the studies was conducted at the Royal Marsden Hospital in England; the other at the European Institute of Oncology in Italy. Together, these two studies had more women on tamoxifen much longer than the American study where only 25% of the participants took the drug five years or longer. Unlike the American study which was halted before long-term effects could be discovered, these studies are ongoing so as to get a picture of what tamoxifen does in the long run. Although both the advisory committee and the FDA dismissed them as unimportant, the studies have in fact produced new information about tamoxifen.

It appears that women who take hormone replacement therapy plus tamoxifen may have some benefit. However, some of the data indicate that if a woman took hormone replacement therapy before she entered the study, she is at higher risk for breast cancer. This hints at the yet unexplored interaction between tamoxifen and synthetic estrogens in the environment, including synthetic hormone replacement therapy. At present, no one knows what happens when a synthetic estrogen blocker with estrogenic potential is given to women exposed to synthetic estrogens.

Tamoxifen-Induced Cancer

While no conclusions can be drawn from the study on whether tamoxifen can prevent breast cancer, conclusions can be drawn about tamoxifen's ability to cause endometrial cancer. About a thousand published studies deal with tamoxifen and endometrial (or uterine) cancer. An analysis of several large studies shows that tamoxifen approximately doubles a woman's risk for uterine cancer when used for one to two years, and quadruples it at five years. While this may be an acceptable risk for women diagnosed with breast cancer (or a woman without a uterus), it is an unacceptable risk for healthy women with no evidence of cancer.

Early on in the Marsden trial, one hundred eleven women were examined for evidence of uterine changes. All of them had increased cell growth. Thirty-nine percent had evidence of abnormal cells, with 16% having abnormal cell growth, and 8% having polyps. In another study at City of Hope, endometrial changes were seen in 35 women taking tamoxifen for breast cancer. Polyps were found in 23. Eleven underwent hysterectomies.

Tamoxifen is also associated with stomach and colorectal cancer. Some data indicates that prior treatment with hormones adds to this risk. What is especially chilling is the likelihood that the risk of cancer with tamoxifen may be a function of total lifetime dose. In other words, the longer you take it, the higher the risk. Women taking tamoxifen longer than five years are reported to have a high incidence of various cancers. Despite the statistics Dr. Norman Wolmark, head of the study, advises women to start taking tamoxifen as soon as they discover they are at high risk for breast cancer. Don't wait, he urges. Age thirty-five has been designated as the age to start worrying.

Faulty Risk Assessment

One of the factors that sets the two European studies apart from their American counterpart is who was enrolled. The Marsden study only enrolled women with a family history of breast cancer. Family history is presently the best standard for risk assessment.

The Italian study went the other way and enrolled women who had no known risk. Because of tamoxifen's propensity to cause uterine cancer, the Italians only accepted women with hysterectomies. By including women who ranged from high risk to possibly no risk, the two European studies covered a much broader cross-section of women than the NCI study that was limited to mostly white women with certain characteristics.

In contrast to the European trials, the NCI trial assigned risk through the "Gail model" for women under 60. Women over 60 were automatically considered high-risk. Neither method of risk assessment is proven. The Gail model is a kind of statistical gambit developed by a group of statisticians at NCI in the late '80s as a way to assess theoretical risk of breast cancer. (It's called "Gail"

after one of its creators, Mitchell Gail). The Gail model was developed from data on 2,800 white women, and it's interesting to note that the same people who criticize the 3,500-person European studies as being too small to be meaningful have no problem relying on Gail for data.

The original Gail model assumes four risk factors for breast cancer: age of menarche, number of breast biopsies, age of having first live birth, and number of first-degree relatives with breast cancer. It takes into account two ages only: over and under 50. It assigns relative risk to each factor by translating a statistical model into more numbers that are multiplied together to get a final "risk" number. The whole exercise has been criticized by groups at MD Anderson and Harvard. For one thing, it overstates risk.

An upgraded Gail was developed to promote tamoxifen. Women will find it challenging to escape high risk under this new-and-improved version. Merely having a child, for example, adds risk for women 40-50. Gail is like a board game. Sample: "if a woman is 35 to 40, she is at high risk if she either has two first-degree relatives with breast cancer and one breast biopsy herself or two benign biopsies (one showing atypical cell growth) and one first-degree relative with breast cancer."

Like a large tuna net, Gail sweeps in everything-and dredges for more. For ages 35 to 59, a woman assesses her risk through "the game." Then, at age 60, Zeneca's version of Gail merely states that the risk is "five year predicted risk of breast cancer of 1.67% as calculated by the Gail Model." This cryptic instruction has led the media and doctors alike to assume that all women over 60 are automatically at high risk. This faulty assumption also underlies the NCI study on which tamoxifen's approval was based. Assuming that every woman over 60 is automatically at high risk for breast cancer is great for market share, but it's scientific voodoo.

The original creators of Gail cite "three major sources of uncertainty" about their risk model. One of those uncertainties is that no one really knows what the risk factors for breast cancer are. That's right-according to its original authors, Gail is partly guesswork. However, Zeneca Pharmaceuticals doesn't mention any uncertainties in its 30-page "information brochure" for busy doctors. Statistical uncertainties have given way to "user-friendly" guidelines that may doom some healthy women to cancers they wouldn't have otherwise gotten.

The Gail model cannot be reliably used to assess risk in the average individual, yet neither the FDA nor Zeneca has informed the public. One of the reasons is that data for the Gail model of risk came from 2,800 women who met specific criteria for entry into a study. They had to be white. They had to live close enough to a participating hospital to conveniently get there. They could not be taking hormone replacement therapy or contraceptives. They had to have no history of blood clots and other conditions. This is not the average woman. To claim that it could be used to assess risk in the average woman is simply untrue.

In addition, the sample size used to create Gail is far too small and far too limited to be applied to the average woman-let alone each woman individually-as Zeneca would have doctors believe. As the creators themselves wrote: "If one had followed large numbers of patients with each possible combination of risk factors, one could estimate the absolute probability of developing breast cancer separately for each risk factor combination from standard life-table methods." They did not. Nor has anyone been able to come up with a genuine risk assessment tool for breast cancer in the average woman. The reality is that women who base their cancer risk on Zeneca's informational brochure are relying on what is essentially a marketing tool-not science.

Potential for New Cancers

In rats and mice, tamoxifen activates liver enzyme cytochrome p450 like most other chemical carcinogens. This originally led researchers to believe that tamoxifen would be a classic carcinogen. However, it was later shown that tamoxifen is metabolized differently in humans than in rats. Tamoxifen does not appear to be a liver carcinogen in humans. However, researchers in Japan did CT scans on the livers of 66 patients taking tamoxifen for three to five years, and found that 36% of them had a fatty liver. The condition was not readily detectable: liver enzymes were elevated in only about half of the women. The researchers recommended regular scans for women taking tamoxifen, yet neither the FDA nor Zeneca has alerted women.

Damage to the p53 tumor suppressor gene has been demonstrated in animals given tamoxifen. Whether this occurs in humans is not known. Tamoxifen also induces cancer genes in rats. But, again, this data is not available for humans. Monkeys given tamoxifen for a week show far less DNA damage than what shows up in rats. And when human liver cells are treated with tamoxifen, they also exhibit far less DNA damage than what occurs in rats. While less DNA damage is better than more DNA damage, it does not equate with no DNA damage. Damaged DNA is a feature of cancer, and should be further investigated before tamoxifen goes into healthy women.

One very troubling aspect of tamoxifen treatment of healthy women is the effect pretreatment with tamoxifen chemotherapy might have on cancer should it subsequently develop. There is concern that tamoxifen pretreatment might make a cancer more aggressive or harder to treat. Particularly regarding the genetic mutation known as BRCA, questions remain as to what tamoxifen can do. BRCA is a DNA repair gene. The effect of taking a DNA-damaging drug on top of a mutated repair gene is not known. There are also unanswered questions about what effect pretreatment might have on a person's ability to respond to chemotherapy should cancer subsequently develop. None of these questions were answered in the one study on which approval was based.

Other concerns are present. Tamoxifen is an estrogen blocker. Estrogen is a chemical messenger throughout the body, not just in the breast. The brain, gut, lung, liver and other organs have estrogen receptors. No one currently knows the effect of long-term suppression of estrogen on these organs. Paradoxically, tamoxifen also has estrogen promoting potential (which may account for its ability to cause endometrial cells to grow). What effect blocking estrogen on one hand, and promoting it on the other, will have on various organs in the long-run is not known.

Scientists have been able to create tamoxifen-dependent tumors in rats. They wrote in a 1993 report: "following cessation of tamoxifen administration, almost one-third of the tumors regressed and more tumors appeared. Resumption of tamoxifen administration resulted in regrowth of some tumors and regression of the new tumors."

Estrogen is crucial during pregnancy. Levels rise and fall at specific time intervals. No one knows whether tamoxifen can affect a future pregnancy. Tamoxifen was originally considered as a birth control pill because it interferes with the ability of the uterus to sustain a pregnancy. It is not clear whether tamoxifen's effects cease when a woman stops taking it. The work of a prominent tamoxifen researcher indicates that tamoxifen's effects are long-lasting. Could it affect pregnancy? Nobody knows.

Putting a Face on Approval

One might ask why tamoxifen was approved when so many serious questions remain. The FDA didn't approve tamoxifen by itself. It had help from a group known as an "advisory committee." By law, advisory committee members are not supposed to have financial interests in the company that manufactures the drug they're advising on. In addition, advisory committees are supposed to be made up of people with "diverse professional education, training and experience." This is so that they bring different points of view to the table. In recent years, advisory committees have recommended approval for a number of dangerous drugs. The public should be aware that participants in the approval process are frequently paid consultants to drug companies.

The committee that endorsed tamoxifen was composed of 11 people, eight of whom are doctors who routinely test chemotherapies. Some, including Richard L. Schilsky, Derek Raghavan and Robert F. Ozols, accept grants from drug companies. Others such as Kim A. Margolin, Kathy S. Albain and Janice P. Dutcher test chemotherapeutic drugs with taxpayer money through the National Cancer Institute (NCI).

The tamoxifen committee represented very little diversity. Its role as an independent body was also questionable. Ozols and Schilsky have both collaborated on studies with doctors who conducted the tamoxifen study. One of the committee members, Richard Simon, works at the National Cancer Institute, which conducted the study.

Simon is a typical example of the type of person currently sitting on advisory committees. A statistician by training, Simon's forte is numbercrunching-not breast cancer.

In the past, Simon argued for not stopping trials early. In an editorial published in the *Journal of Clinical Oncology*, he used the example of clofibrate to illustrate his point. (Clofibrate is a cholesterol-lowering drug whose effects appeared promising during the early stages of the Coronary Drug Project. If the study had been prematurely stopped, as the tamoxifen study was, the real picture would not have emerged: clofibrate is no better than placebo in reducing heart-related mortality. By the end of the study it was shown that clofibrate caused a 44% increased mortality from cancer and other causes). Studies must not be stopped early, Simon argued. His pen-and-ink arguments melted away, however, when it came to tamoxifen, which he supported.

The public expects committee members to be impartial. Yet before he ever sat on the tamoxifen committee, Simon had attacked data showing tamoxifen causes increased risk of colorectal and stomach cancer. The motivation for the attack is not known. He failed to respond to a request to clarify his position.

Fraudulent Studies

The study on which tamoxifen was approved for healthy women has a lurid history. A surgeon named Bernard Fisher was the driving force behind tamoxifen's approval as a preventative agent. Fisher began conducting studies on tamoxifen in the early '80s under the taxpayer-funded NSABP. The project, which he headed, was receiving about \$18M a year in federal money when NCI decided to spend \$68M to see whether tamoxifen would prevent breast cancer. Fisher was to coordinate the massive project which began in 1992.

In 1990, it was discovered that a doctor participating in NSABP trials had falsified data for 99 people enrolled in 14 breast cancer studies that preceded the prevention trials. Fisher was accused of not reporting the falsification, then using the data in an article published in the *New England Journal of Medicine*. In 1993, it was discovered that secretaries in charge of enrolling women at a hospital participating in the breast cancer prevention trial had manufactured data. One of them was receiving \$250 a head for each woman she enrolled. The fraud was discovered during a routine audit, and Fisher's office was notified. Apparently Fisher buried the report and never told NCI. A few months later, a woman named Hazel Cunningham, who wanted to enroll in the tamoxifen prevention trial, discovered that the consent form being used by Fisher didn't inform women about the true number of uterine cancer deaths

occurring in the cancer trials. She filed a petition to stop the trials.

Representative John Dingell began congressional hearings into the NSABP, and Fisher was stripped of his position. The trials were halted. Although Fisher refused to appear at hearing-citing medical problems-he had enough fortitude to file lawsuits against five federal agencies, their directors, and the University of Pittsburgh. A federal judge threw out the case against the agencies in 1996. After much wrangling Fisher, who admitted knowing about the fraudulent data but felt the study would have been hurt if he eliminated it, was exonerated by an investigative arm of the Department of Health and Human Services which has been accused of favoring big-wig researchers. His case against the University of Pittsburgh was settled, and he was ultimately paid money and reinstated on the study. A judge also ordered the NCI to quit flagging his research as unreliable.

FDA Review Falls Short

In light of all that had occurred, the FDA had valid reasons to carefully review all the data from the prevention trial. It did not. In fact, the agency may have set a record for fast review. According to Dr. Susan Honig who was in charge, the FDA received the final data on tamoxifen on August 4th, four weeks before the advisory committee hearing on September 2nd. Originally, the FDA was sent submissions missing crucial data. According to the transcript of the advisory committee hearing, the agency reviewed 625 of the 6681 case report forms of the women who got tamoxifen. (Case report forms are the actual record of what occurred to the patient, as filled out by healthcare workers who actually interacted with her. This is distinct from data summaries created by the drug manufacturer). Reviewing case forms is important, as numerous investigators on drug trials have been caught falsifying data. Given that it was already known that data had been falsified in tamoxifen trials, it would seem crucial for the FDA to review a substantial number of the case report forms. Instead, it held a committee meeting four weeks after receiving data from the trial, and announced its approval four weeks later.

Committee Rejects Monitoring of Women on Tamoxifen

One might wonder how a committee that refused to endorse the statement that tamoxifen has a favorable risk/benefit ratio for the prevention of breast cancer would ultimately approve tamoxifen for the prevention of breast cancer. The answer lies in semantics. A review of the record shows that the committee refused to use the word "prevention" but reframed the issues until they could recommend approval. The actual recommendation of the committee is that tamoxifen be approved for the "risk reduction of the short-term incidence of breast cancer in women at increased risk as defined by the study population." Despite the refusal of the committee to recommend tamoxifen for prevention, the American Cancer Society and the media immediately hailed tamoxifen as a breast cancer prevention drug.

And despite evidence that tamoxifen causes endometrial cancer, the committee rejected advising women to undergo endometrial testing while on tamoxifen. During the discussion among committee members, George W. Sledge Jr., a drug researcher, stated his belief that such testing would be nothing more than an employment act for OB-GYNs. The committee agreed with Sledge and voted not to warn women to have endometrial testing. They also nixed yearly eye examinations for cataracts. The issue of warning women about blood clots never came up, although the committee felt the FDA should ask someone to look into it further.

After the committee finished with tamoxifen, they went on to another hearing about the drug, Herceptin. Drs. Schilsky and Raghavan's conflicts-of-interest were duly noted for the record.

While the hype sounds good, tamoxifen has not been proven to prevent breast cancer. Two studies show it doesn't, and numerous studies show it increases a woman's risk of endometrial cancer. Everyone would like to believe that merely taking a pill will keep them from getting cancer. Unfortunately, such a pill has never been invented. There are steps, however, that a woman can take to decrease her risk of breast cancer that do not involve drugs.

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