TAMOXIFEN QUANDARY

Promising cancer drug may hide a troubling dark side

By JANET RALOFF

In January, an international team of researchers published a huge analysis of the success of various post-surgical, or adjuvant, therapies for breast cancer. Drawing on 133 randomized trials from around the world, their data identified tamoxifen – a synthetic hormone – as the ascendant star.

Unlike standard chemotherapeutic agents – which kill dividing cells throughout the body, not just in the cancer – tamoxifen kills nothing. It routs cancers by starving them of the estrogen that can promote their growth.

Hailed as nothing less than a wonder drug, tamoxifen has proved so successful in stalling or preventing breast cancer recurrence that researchers in the United States stand poised to begin large-scale trials of the drug this week in healthy women at high risk of the disease. A related trial could begin any day in the United Kingdom, with others slated in Europe and Australia. Their goal: prevention of breast cancer – the most common malignancy in women.

New toxicological studies, however, hint that tamoxifen may itself cause cancer. These findings are seeding doubts about the wisdom of administering the potent anti-estrogenic drug for years – perhaps for life – to healthy women.

The new data have already held up the U.K. cancer-prevention trial involving tamoxifen. On March 12, as the study's leaders planned to begin recruiting an estimated 13,000 additional volunteers for a scaled-up five-year program, Britain's Medical Research Council (MRC) withdrew its support for the study as currently designed, pending further toxicological studies. The two remaining sponsors – the Imperial Cancer Research Fund and the Cancer Research Campaign – decided to continue the trial on their own, provided the U.K.'s Department of Health approves. At press time, that agency was taking a second look at the study design.

A U.S. tamoxifen trial for breast cancer prevention, funded by the National Cancer Institute (NCI), remains on track. NCI has scheduled a press conference for April 29 to announce details of this study, slated to eventually involve 16,000 healthy, high-risk women age 35 and over, half of whom will get the drug.

MRC Secretary Dai A. Rees explained his agency's decision to withdraw from the U.K. study in the March 28 BRITISH MEDICAL JOURNAL. Unpublished data by tamoxifen's manufacturer indicate that the drug induces liver tumors in rats, he notes. Because of the way it accumulates in the human body, doses of the drug responsible for producing cancers in rats appear "similar to those to be used in the trial," Rees says. As a result, "there is no dose or safety margin."

Rees also cites a study reported in the March 1 CANCER RESEARCH showing that tamoxifen produces potentially carcinogenic DNA alterations – known as adducts – in the livers of at least two types of rodents. Finally, though researchers have studied tamoxifen's effects in thousands of women, few of those patients have received the drug for more than five to seven years; that's less time than it usually takes for carcinogens to induce liver tumors in humans, Rees notes.

Worldwide, breast cancer rates are increasing (SN: 4/21/90, p.245). This disease, which will strike one in nine U.S. and Canadian women sometime during their lives, kills almost 45,000 each year in the United States alone.

MRC "has no wish to spread alarm among women taking tamoxifen for proved breast cancer," Rees says; for them, tamoxifen "is a well-tried and effective treatment" (see sidebar). However, until potentially life-threatening side effects can be ruled out, he says, MRC cannot justify administering this drug, as planned, to healthy women under age 40.

But not all researchers regard the new animal data as particularly revealing about tamoxifen's threat to humans. "Rat experiments seem to be the first stage, used to try to decide whether to use a drug or not," says Richard Peto, director of the cancer studies unit at Oxford University in England. "But once you've tried it for several years in tens of thousands of women, why not just look at what

For women with breast cancer . . .

Among women over age 70 with breast cancer, tamoxifen faces "no competition," according to Richard Peto, who led the two-part analysis of adjuvant therapies for breast cancer published in the Jan. 4 and 11 issues of LANCET (SN: 2/22/92, p.124). Among these older women, for whom traditional cell-killing chemotherapy drugs usually prove too toxic, tamoxifen "delays cancer recurrence substantially and delays death substantially," he reports, "And the longer you treat the women, the greater the benefit."

Among breast cancer patients in their 50s and 60s who received the drug, Peto observes, tamoxifen works somewhat better than conventional chemotherapy, produces far less devastating side effects and lowers significantly the death rate from breast cancer. Peto acknowledges that more aggressive chemotherapy treatments have emerged since many of the studies that he analyzed were undertaken. However, he asserts, tamoxifen remains "at least as good" as the newer chemotherapies.

Moreover, tamoxifen doesn't really compete with these chemotherapies, he says, because use of one does not rule out use of the other. Indeed, used together, their effects appear additive.

However, roughly 20 percent of women who develop breast cancer are under age 50. For them, tamoxifen "is still just a research thing," he says. Though data are not yet available to establish how well the drug works in them, Peto says, "I suspect the answer will be much the same as in older women."

"I think there's pretty clear evidence that for women with breast cancer, [tamoxifen] is doing more good than harm," he concludes.

Few clinicians or toxicologists would argue. Opinions tend to diverge only over how the scales may tip in weighing the drug's costs and benefits for healthy women. *– J. Raloff*

you see there? And [with tamoxifen], what you see is that, overall, benefits outweigh harm."

Oncologists and surgeons designed the tamoxifen cancer-prevention trials, points out Adriane Fugh-Berman, a physician in Washington, D.C. "And to them," she says, "tamoxifen is like a vitamin – it's the least toxic oncology drug they deal with.

"But those of us in preventive health and medicine have different standards about what kinds of things you should unleash onto a healthy population," she maintains. Ideally, she says, programs targeted at healthy, at-risk people "should be extremely safe – preferably health promoting. And if not health promoting, at least nontoxic."

Several researchers, including Peto, argue that tamoxifen is just that – relatively nontoxic and health promoting. In older women diagnosed with breast cancer, tamoxifen reduces cholesterol levels in the blood by about 20 percent, increases bone density and appears to prevent new primary cancers in the other breast. On the positive side of the risk-benefit equation, he concludes, the drug not only prevents breast cancers, but also reduces the risk of heart disease and osteoporosis.

However, a few studies have indicated an increased risk of endometrial cancer among women on tamoxifen. There is also "compelling evidence" that the drug's active metabolite in the body – 4-hydroxytamoxifen – stimulates the growth of human endometrial cancer cells grown in culture, notes Liam J. Murphy of the University of Manitoba in Winnipeg.

In the April 1 CANCER RESEARCH, he and his co-workers report finding that "this growth-stimulatory effect was observed at very low concentrations . . . [and] was specific to [tamoxifen], since the other anti-estrogens tested did not stimulate [cancer-cell] proliferation." These data certainly suggest that tamoxifen might pose a cancer risk to women in the upcoming prophylactic trials, Murphy told SCIENCE NEWS.

However, Peto notes, caught early, endometrial cancer seldom kills. As such, he asserts, "it's no big deal."

Fugh-Berman reaches a different conclusion. "It really freezes my blood when people say endometrial cancer is not a bad cancer," she says. "The treatment for it is hysterectomy, and to some of us, it is a big deal to lose your uterus." Moreover, she says, "the way you detect it is by endometrial biopsy, which not everybody will be willing to undergo annually; they're quite painful." She also cites evidence that tamoxifen can increase a woman's risk of thrombophlebitis, which can lead to life-threatening pulmonary embolisms.

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"We're afraid these tamoxifen intervention trials are really going to set a precedent for experiments in disease substitution – a concept we don't like," she told SCIENCE NEWS. Until the drug's long-term safety has been established, she says, the National Women's Health Network, of which she is a board member, will object to tamoxifen's use in healthy populations. At a minimum, she'd like to see the drug's ambiguous liver cancer status resolved.

So would Lars E. Rutqvist, an oncologist at the Karolinska Institute in Stockholm, Sweden. To date, his team remains the *only* one to report evidence of a possible increased risk of liver cancer in women on tamoxifen.

In the Jan. 21, 1989 LANCET, Rutqvist and his co-workers reported finding two primary liver cancers among women taking tamoxifen in a randomized Swedish trial – an incidence four times the expected rate.

Why have no other researchers turned up similar cancers? "This is really puzzling," Rutqvist says, because other studies haven't even observed what has been the normal incidence of this relatively rare malignancy.

Fugh-Berman has one idea: Clinicians can't find what they don't look for. "There are a lot of women who take tamoxifen for breast cancer, but they're not routinely autopsied." And even if doctors detect a mass on the liver, she says, "some clinicians may call it a metastasis [spawned by the original breast cancer]. They should be biopsying it to determine whether it's really a second [and unrelated] primary cancer caused by the tamoxifen."

Gary M. Williams, medical director of the American Health Foundation in Valhalla, N.Y., shares her view. "I've specifically asked clinicians if a woman receiving tamoxifen has a liver mass, will they work her up to see if it is a liver cancer versus a metastasis from the breast," he says. "And the answer has always been, 'No. We assume it's a metastasis.'" With that attitude, he says, "no one knows what the incidence is of liver cancers in tamoxifen users."

But there is growing reason to worry, many scientists believe. For instance, a paper in the Nov. 15, 1991 CANCER RESEARCH showed that in the livers of rodents, tamoxifen produces metabolites that react very strongly with proteins. "We don't yet know what this reactive [metabolite of tamoxifen] is, but we know it binds irreversibly," says study coauthor David Kupfer of the Worcester Foundation for Experimental Biology in Shrewsbury, Mass. These data, adds Williams, suggest that "tamoxifen is being handled in the liver like a chemical carcinogen, not like a hormone."

A growing body of toxicological research suggests that most chemical carcinogens cause their damage by binding to DNA, forming adducts. And in the March 1 CANCER RESEARCH, chemists at the University of Texas Medical Branch in Galveston report finding novel DNA adducts in the livers of rats and hamsters fed tamoxifen.

Ordinarily, the body can repair much, if not all, of this type of damage. What proved startling, recalls Joachim G. Liehr, who led the study, "was not that the tamoxifen causes DNA damage – many drugs do – but that with repeated administrations of the drug we seem to get fairly little repair." After all, he notes, "tamoxifen is being touted as a 'safe' drug that can be taken for many years with few side effects. Because of this reputation, I expected to see little DNA damage. In fact, we found a lot."

Liehr was also surprised to find that he could not prevent the formation of DNA adducts in the liver by administering either vitamin C or another chemical to the animals. In previous trials with a related anti-estrogenic drug – diethylstilbestrol (DES) – both treatments quashed adduct formation.

Taken together, these data "may make this drug a poor choice for the chronic preventive treatment of breast cancer," Liehr and his coauthor, Xueliang Han, conclude.

But Leslie G. Ford, chief of community oncology and rehabilitation for NCI, argues that "it's misleading to say [adducts] mean DNA damage because there's no evidence that they have been incorporated into the genome."

While Williams agrees that there is no direct evidence, he says a pair of unpublished, just-completed studies appear to offer indirect evidence of the adducts' carcinogenicity.

Having himself demonstrated DES' ability to induce liver tumors in animals, Williams decided to investigate a structural analog – tamoxifen – and toremifene, another anti-estrogenic breast cancer drug.

Unlike toremifene, which produced no tumors, tamoxifen proved to be "a riproaring liver carcinogen," Williams says. At the higher doses studied, within one year it produced cancers in 100 percent of the treated animals, something he describes as "an astonishing effect."

"These are massive liver tumors," Williams told SCIENCE NEWS. "This is the strongest liver cancer effect that I have seen with a chemical carcinogen."

The natural expectation, he recalls, was that any carcinogenic effect from tamoxifen would trace to the drug's binding to estrogen receptors. But when toremifene, which binds to those same receptors, produced no cancers, "we became perplexed." Then along came Liehr's paper. "I now think it provides a very convincing explanation for the [induction] of our tumors," Williams says.

He also conducted a lower-dose experiment in which animals received just 10 times the tamoxifen dose typically administered to women. "And in one year, we got precancerous lesions," Williams says. Rutqvist reports that representatives of a Finnish pharmaceutical firm told him they also have produced precancerous liver changes – called hyperplasic nodules – in nearly 100 percent of their tamoxifen-treated animals. Rutqvist is now considering looking for evidence of similar precancerous changes in autopsy tissues obtained from Swedish women who had taken tamoxifen.

Nor are endometrial and liver cancers the only malignancies that have been linked with tamoxifen.

Some small percentage of breast cancers do not appear dependent upon hormones for their growth. In the Jan. 1 CANCER RESEARCH, Karin C. Fendl and Stephen J. Zimniski of the University of Miami School of Medicine report finding that tamoxifen-treated animals, compared with animals given no treatment, had an excess of these hormone-*independent* malignancies – aggressive cancers that are very resistant to treatment.

The Miami team used the classic animal model for human breast cancer: Rats fed the carcinogen dimethylbenzanthracene (DMBA) once a week for four weeks develop palpable mammary tumors just under the skin.

Nine weeks into one experiment, the researchers began administering 1 milligram of tamoxifen per kilogram of body weight to half of their animals. After three weeks, 70 to 90 percent of the DMBA-induced tumors had shrunk in size. In a second trial, where DMBA and tamoxifen were administered together for four weeks, animals receiving the combo treatment developed far fewer breast cancers than rats receiving DMBA alone.

That's the good news. The bad news is that in both trials, "every [new] tumor that appeared in a tamoxifen-treated animal was subsequently found to be hormone-independent," the Miami researchers report. A small percentage of the breast tumors in rats administered DMBA alone also proved hormone-independent. However, hormone-independent tumors grew three times faster in the tamoxifen-treated animals – "doubling in size daily," notes Zimniski, now at the University of Kansas' Women's Research Institute in Wichita. "We've never seen tumors grow that fast."

How does that translate to women?

A few weeks ago, Rutqvist says, "the first data came out of our computer suggesting that women with hormone-independent tumors do worse when they receive tamoxifen than when they don't."

Defining the women at high risk

In general, breast cancer risk increases with age. The prophylactic tamoxifen trials will recruit healthy women who face a relatively high risk of developing breast cancer – generally defined as a risk at least equal to that faced by the average, healthy 60-year-old woman. According to NCI's Leslie G. Ford, this translates to a nearly 2 percent chance of developing the cancer within five years.

	Relative risk		% probability of disease within 10 years of		
Risk factor	**age < 50**	**≥ 50**	**age 40**	**50**	**60**
None	1.0	1.0	1.2	1.6	1.8
One biopsy	1.7	1.3	2.1	2.0	2.3
One relative (mother or sister)	2.6	2.6	3.2	4.0	4.6
One relative, one biopsy	4.4	3.3	5.4	5.1	5.8
One relative, one biopsy, first birth at age 30	4.8	3.6	5.9	5.5	6.3
One relative, one biopsy, first birth at age 30, menarche at age < 12	5.8	4.4	7.0	6.6	7.5
One relative, two biopsies	7.5	4.2	9.0	6.4	7.3
One relative, two biopsies, first birth at age 30	8.2	4.6	9.7	7.0	7.9
One relative, two biopsies, first birth at age 30, menarche at age < 12	9.9	5.5	11.6	8.4	9.5
Two relatives, one biopsy	11.5	8.7	13.4	12.7	14.4
Two relatives, one biopsy, menarche at age < 12	13.9	10.4	15.9	15.2	17.1
Two relatives, two biopsies	19.6	11.0	21.8	15.9	17.9
Two relatives, two biopsies, menarche at age < 12	23.6	13.3	25.5	18.7	21.0

Adapted from Nayfield *et al.*, J. of NCI, Oct. 16, 1991.

As the chart shows, certain family-history characteristics can significantly increase risk – and the likelihood that the cancer will strike prior to menopause. Among them: having a mother or sister with a history of breast cancer, bearing one's first child after age 30, undergoing menopause after age 45 (especially after age 55), experiencing menarche (the onset of menstrual periods) before age 12, and having a history of at least one biopsy for benign breast disease.

"One of our objections [at the National Women's Health Network] to the coming [prophylactic] trial is that in order for the researchers to get enough volunteers, they've cast their net very broadly," charges Washington, D.C., physician Adriane Fugh-Berman. "They are including women who are not at very high risk, but essentially healthy women."

Next month, her organization plans to develop its own table, essentially a chart comparing what the designers of the NCI-sponsored study consider high risk "versus what we think is high risk," Fugh-Berman says. "We think it will be a tool to help women make more informed decisions on whether to participate." – *J. Raloff*

The findings come from a very small subgroup – about 350 of the roughly 1,800 postmenopausal women he's studying.

"We don't know whether the finding is due to chance," he says. "But clearly, we'll be observing this group closely to see whether the trend continues with increasing follow-up."

His data also hint of a possible small increase in gastrointestinal cancer among tamoxifen users. Ordinarily, he says, he probably would not pay much attention to such a trend – except that another Swedish study and a Danish trial have identified signs of a similar small increase in gastrointestinal cancer among women receiving tamoxifen as adjuvant therapy for breast cancer.

Overall, Rutqvist finds a small increased risk of cancer in women receiving tamoxifen: Roughly 8 percent develop new, primary cancers of all kinds, compared with about 5 percent among the controls (postsurgical patients receiving no hormonal therapy). He plans to report these findings in May at a meeting of the American Society for Clinical Oncology.

Rutqvist's group has conducted one of the longest tamoxifen trials. Women in this ongoing program, which began in 1976, receive 40 mg of the drug daily.

Seven years ago, researchers at the Royal Marsden Hospital (in London and Sutton) began quite a different long-term tamoxifen trial – this one directed at assessing whether researchers could learn anything from giving 20-mg prophylactic doses daily. Some 1,500 women – healthy but with a high overall risk of breast cancer – have entered their study so far. Another 10 to 15 recruits join the program each week.

Among the women receiving tamoxifen in this trial, "we've not seen any evidence of an increased risk of second cancers," says Trevor J. Powles, one of the study's leaders. However, he acknowledges, "it's arguable that it's still too early" to see such an effect.

Powles is not particularly worried about the new animal data. "I find it remarkable that people are still looking at rat data, which are generally irrelevant anyway," he says. "I think the human data now are the critical factor."

Adds NCI's Ford: "We've known about liver cancer in rats for many, many years. [The new toxicological studies] really don't add anything new to that."

Moreover, she says, the National Surgical Adjuvant Breast and Bowel Project – the network of more than 200 research centers throughout the United States that will conduct the NCI-funded U.S. cancer-prevention trial involving tamoxifen – "went to the world's experts on determining breast cancer risk."

The resulting risk-benefit analysis indicated that the U.S. trial might carry some low risk of fostering endometrial cancers – and even liver cancers, acknowledges Ford, who will oversee the new trial for NCI. But after weighing these risks, the Food and Drug Administration determined that on balance the U.S. trial "still looks like it's worth doing" – and indeed is something it "felt comfortable with," she says.

What's more, prospective recruits will be informed of the potential risks associated with entering the study. Indeed, Ford says, "I want to go on record saying this is probably one of the most comprehensive informed-consents we've ever seen. Every comment that FDA made was taken into account."

Drug therapy to head off breast cancer in high-risk but healthy women "is a different type of clinical trial than anything that's been done before – certainly in cancer," Powles says. When the United Kingdom's large-scale prevention trial gets underway, another 13,000 women will join those being studied at Royal Marsden. Powles' hope: to cut the risk of breast cancer in these women by half, maybe more.

"We have an opportunity to prevent breast cancer, certainly by a substantial amount. No one can tell me we can do that without taking a few chances," Powles concedes. "But I don't think we could have gone into this more cautiously than we have . . . and I don't think we'll ever get anything better." □