FDA, others offer new tamoxifen warnings

The Food and Drug Administration announced new data that it says justify stronger warnings to doctors and women about the cancer risks associated with tamoxifen. This synthetic hormone is the most effective drug for preventing new malignancies in women who have had breast cancer.

While unveiling new toxicological data on the drug, several researchers sounded additional warnings this week in San Francisco at the annual meeting of the American Association for Cancer Research (AACR).

The FDA announced late last week that, with the agency's encouragement, tamoxifen's maker – Zeneca Pharmaceuticals of Wilmington, Del. – would send letters to 380,000 health care professionals. Also called for by the Washington, D.C.-based National Women's Health Network, this mailing alerts physicians who might prescribe tamoxifen to new risk data that will be included in the packaging of the drug.

Zeneca's letter notes, for instance, that breast cancer patients randomly assigned to receive tamoxifen in a 9-year Swedish study developed almost six times as many endometrial cancers as did participants taking a placebo, or inactive substance. Earlier this year, a U.S. study reported 11 times more endometrial cancers in breast cancer patients assigned at random to receive tamoxifen (SN: 2/26/94, p.133).

"Our biggest concern," explains Robert DeLap of FDA's oncology division in Rockville, Md., "is this endometrial cancer, because it is an illness that certainly can be dangerous." Indeed, some data suggest that such tamoxifen-induced uterine cancers may be unusually deadly (SN: 9/25/93, p.207).

Last week, FDA Commissioner David A. Kessler advised women who have used tamoxifen to get regular gynecologic exams and report immediately any abnormal vaginal bleeding or discharge.

Zeneca also reports adverse reproductive changes and cancer in animals whose mothers received tamoxifen. Because the changes resemble those seen in the offspring of animals and women taking diethylstilbestrol (DES), FDA and Zeneca ask doctors to "stress that women should not become pregnant while taking [this drug]." Finally, Zeneca's letter to doctors hints at increased risk of gastrointestinal cancers in the Swedish trial's tamoxifen users – something first noted 2 years ago (SN: 4/25/92, p.266).

A good model for cancer studies is mouse skin. It contains all the enzymes needed to metabolize, or activate, toxic chemicals into forms that can bind to – and alter – DNA, note toxicologists Hua Chen Wei and Qiuyin Cai at the University of Alabama at Birmingham.

Because tamoxifen has long been used to fight breast cancer, Wei expected it to block the production of adducts, or metabolites bound to DNA, in mouse skin exposed to a classic carcinogen. Instead, he reported at AACR, the drug resulted in the creation of four novel adducts in the cells under study. His team will investigate whether tamoxifen adducts can lead to tumors. If they do, he says, "We can assume as a general rule that [these adducts] might do so in other types of cells."

After incubating tamoxifen with both DNA and human liver enzymes, Deena N. Pathak and his coworkers at the University of California, San Francisco, also detected novel adducts.

Though liver cancers have been loosely linked to tamoxifen use, the new data reported at AACR may have more general implications, adds Pathak's UCSF colleague William J. Bodell. The liver activates many toxic compounds that eventually do their harm elsewhere. Therefore, he says, tamoxifen's liver metabolites might travel to form adducts in the uterus. "The major question that needs to be answered now," he says, "is whether [metabolic activation of tamoxifen] occurs in women taking this drug."

Dutzu Rosner, a surgical oncologist from the State University of New York at Buffalo, reported at AACR on another side effect of tamoxifen. The drug spiked the concentration of estrogen in the blood of three of the six young women he studied – to between 3 and 15 times its pretreatment level. Because lifetime exposure to estrogen can prove a risk factor for several reproductive cancers (SN: 7/3/93, p.10), Rosner argues that young women should receive tamoxifen only if they will be scrutinized closely for estrogen increases and endometrial abnormalities by their doctors.

Rosner says his data show "tamoxifen was stimulating the ovaries to produce this estrogen." Because the ovaries shut down estrogen production at menopause, he notes, this risk would trace only to premenopausal use of the drug.

Though Zeneca's compound has been used since the 1960s, these new data "underscore how little we know about tamoxifen," says Trudy L. Bush of Johns Hopkins University in Baltimore.

The new data also weigh in against tamoxifen's use in healthy women, she believes. In NCI's ongoing breast cancer prevention trial, "98 percent of the participants aren't going to benefit from tamoxifen, yet [all 8,000 healthy women slated to receive it] will be at risk for the adverse outcomes." Indeed, she says, "I'm questioning the philosophy of chemoprevention in healthy women using a toxic agent." – *J. Raloff*

Hubble eyes the shapes of distant galaxies

What did galaxies look like when the universe was roughly half its current age? A repaired Hubble Space Telescope has begun to provide the answer.

Hubble's new wide-field and planetary camera now has clearly resolved the shapes of galaxies some 7 billion light-years from Earth, astronomers reported last week. Because peering at distant galaxies is like looking back in time, the images reveal the galaxy types that existed when the universe was 60 percent of its current age, says Richard Ellis of the University of Cambridge in England.

The abundance of spiral galaxies confirms that galaxies like our Milky Way were well established at this early epoch, he adds. Ellis, who collaborated with Richard E. Griffiths of Johns Hopkins University in Baltimore, presented the new images at a joint meeting of the Royal Astronomical Society and the European Astronomical Society in Edinburgh.

Rather than target specific areas of the sky, the camera observes random patches during times when another Hubble instrument points at a predetermined target. Some of the random images reveal only blank areas of sky, but most show about 20 galaxies, Ellis notes.

Because the survey examines galaxies that evolve in relative isolation, as the Milky Way does, it complements another Hubble project, which analyzes the shapes and colors of distant galaxies that reside in crowded clusters (SN: 12/5/92, p.390). The gravitational forces within a cluster can rip galaxies apart or cause them to collide and merge, dramatically altering the course of galactic evolution. But most galaxies in the cosmos have few close neighbors, comments Ellis.

Comparing images of distant galaxies that grow up in a dense cluster with those that go it alone in the cosmos graphically illustrates the environment's role in galactic evolution, he points out. In addition, Ellis says, the abundance of spiral galaxies relative to ellipticals in the survey of distant, individual galaxies should settle the controversy about whether ellipticals arose from the merger of spirals.

The new Hubble camera has collected images of some 300 galaxies since it joined the survey in February. This amounts to more than 10 times as much survey data as the old wide-field and planetary camera gathered during the past 2 years, Ellis notes. The old camera required much longer exposures and could only image relatively bright galaxies because it lacked the corrective optics to compensate for Hubble's flawed primary mirror. Astronauts replaced the old camera with the new one last December. – *R. Cowen*