Beating Breast Cancer

Researchers are looking beyond conventional surgeries and chemotherapy

By DIANE D. EDWARDS

Over the past four decades, the five-year survival rate for women with localized breast cancer in the United States has risen from 78 percent to 90 percent, approaching 100 percent survival with early detection. At the same time, however, the total number of breast cancer deaths has changed little, mainly because the nation's population is aging and therefore at higher risk. And if the cancer has spread, only 60 percent of patients survive for five years. Experts predict more than 135,000 new cases of breast cancer and 42,000 deaths this year.

But researchers seek to tip the scales in favor of hope. At the American Cancer Society's 30th science writers seminar in Daytona Beach, Fla., scientists outlined new efforts to beat the second-leading cause of cancer deaths in women. Some of the studies are controversial or preliminary; others attempt to fine-tune established protocols. Results suggest that using anticancer drug treatment before surgery, doing surgery at specific times and optimizing the effects of the anti-estrogen drug tamoxifen could improve a patient's outcome. Indeed, some researchers now wonder if tamoxifen might help prevent breast cancer in some high-risk women.

Because the hormone estrogen seems to stimulate the growth of certain breast cancers, scientists have long looked for a causal link between the two. Results are contradictory, although recent studies conclude there is no increased risk of developing breast cancer among users of hormone-containing oral contraceptives (SN: 8/16/86, p.100). Still, researchers pay attention to scattered reports suggesting a link between the hormone and cancer.

Anti-estrogen therapy has been used for years in breast cancer patients, particularly the estimated 60 percent whose cancer cells bear estrogen receptors on their surface. Among the most common anti-estrogen drugs is tamoxifen citrate, a synthetic compound that competitively binds to and thus blocks the estrogen receptors.

Despite some successes, however, tamoxifen benefits only half of receptor-positive patients and less than one-third of those treated regardless of their receptor status. And in 4 to 26 percent of treated patients, the anti-estrogen ironically seems to cause a "flare," a poorly understood condition where the cancer goes wild and spreads rapidly through the body.

At the Oregon Health Sciences University in Portland, William S. Fletcher and his co-workers are using the flare phenomenon to learn why anti-estrogen therapy sometimes fails. Fletcher's team began with the hypothesis that a flare occurs when a woman's own estrogen supply "overwhelms" tamoxifen binding.

The authors, after studying hormone levels in 15 patients whose secondary tumors grew during tamoxifen therapy, conclude in their report in the November ARCHIVES OF SURGERY: "Paradoxically, tamoxifen appears to stimulate the adrenal gland to produce [estrogen precursors], which ultimately defeats the purpose of the drug." Because the receptors bind estrogen 10,000 times more avidly than they do tamoxifen, Fletcher says a small increase in the body's production of estrogen is enough to negate the drug's beneficial effects. He told the cancer seminar that, for patients in whom tamoxifen stimulates tumor growth, physicians should discontinue the drug, remove the ovaries and either surgically remove the adrenal glands or suppress them with drugs.

But some cancer specialists feel that removing the adrenal glands (adrenalectomy) is inappropriate. Seminar participant Joseph Ragaz of the Cancer Control Agency of British Columbia in Vancouver told SCIENCE NEWS that other studies find adrenalectomy does not prevent tamoxifen flares. Ragaz maintains it may be that the cancer cells themselves are resistant to the drug treatment.

Whether or not adrenalectomy enters clinical regimens, the idea that adrenal glands play some role "is a very reasonable one and is worthy of further investigation," says Richard R. Love of the University of Wisconsin Center for Health Sciences in Madison. According to Fletcher, Love and his colleagues are doing the type of studies needed prior to a widespread clinical trial testing the suspension of tamoxifen in nonresponding women. Love's work also suggests tamoxifen might prevent breast cancer in healthy women at high risk.

Tamoxifen is primarily used in postmenopausal women with breast cancer to prevent recurrence of the disease after surgery and thus prolong survival. Although long-term therapy is often prescribed, the gamut of possible side effects has not been adequately catalogued, says Love. His ongoing study is assessing the effects of tamoxifen on such things as bone density, blood lipids and blood clotting. Because low estrogen levels have been tied to heart disease and osteoporosis, as well as to menopausal symptoms, tamoxifen's effects must be studied in broader terms than just breast cancer, he adds.

John Laszlo, the American Cancer Society's vice-president for research, calls Love's approach technically difficult, "a very long and arduous kind of task," but one that could answer whether tamoxifen can be used long-term as a cancer pre-

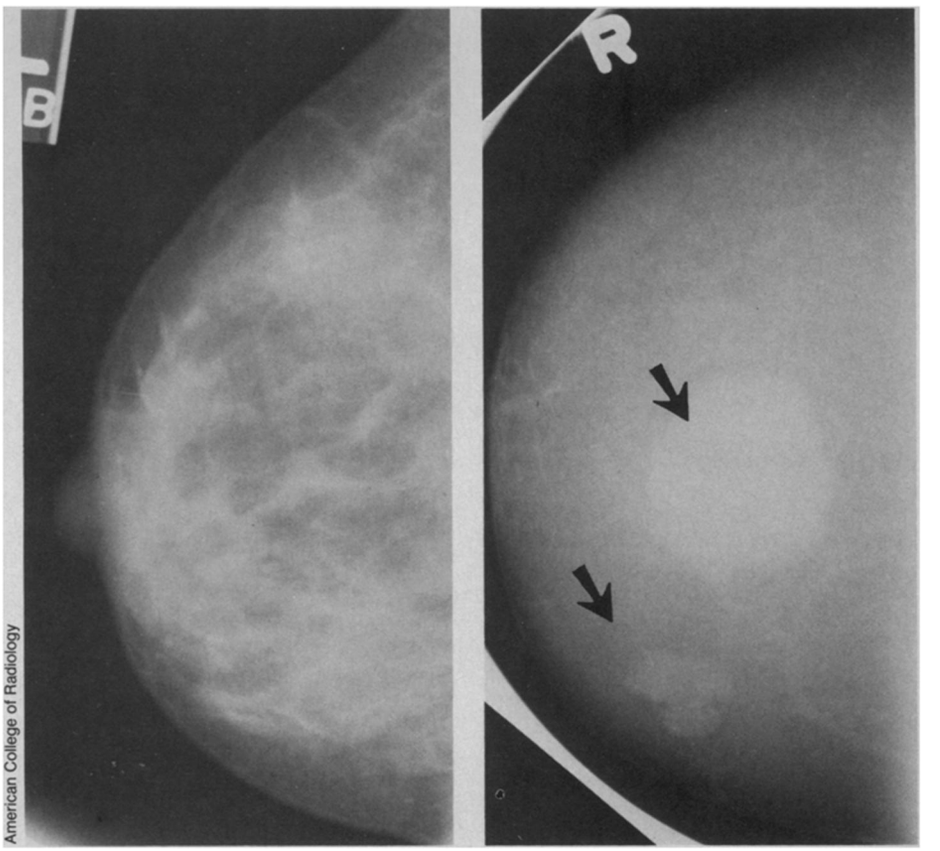
ventive. He considers tamoxifen "a real prime candidate for prophylactic use in women with a high risk for breast cancer." Among those at highest risk are women whose close relatives have had the disease and those who are over 50 years of age. Although the concept of chemoprevention is attracting researchers, Laszlo points out that there has been little success thus far. Among the cancers included in chemoprevention studies are those of the skin and lungs.

In Vancouver, Ragaz and others at the Cancer Control Agency are analyzing the use of chemotherapy *before* surgery for breast cancer, rather than the standard practice of initiating systemic drug treatment after surgery. Called neoadjuvant treatment, this preoperative approach targets micrometastases – tiny tumors caused by cancer cells that spread from the primary tumor. "We treat simultaneously the systemic disease . . . and the big-bully primary [tumor]," says Ragaz.

Neoadjuvant therapy also may shrink inoperable tumors enough to make surgery possible. In a study of about 60 women with advanced breast cancer, up to 90 percent of tumors considered inoperable shrank to operable size, Ragaz says, noting that other U.S. studies have yielded similar results. None of these results should be considered the final word and more complete clinical trials would be needed before physicians embrace the new approach, he adds.

Current treatment regimens call for surgery, followed six to eight weeks later by chemotherapy with such agents as methotrexate or 5-fluorouracil. During that delay, says John P. Minton of Ohio State University in Columbus, cancer cells may break loose and travel elsewhere in the body. Referring to Ragaz's study, Minton says "the hope of the situation" is that these renegade cells would be stopped by drugs given just before or just after surgery. But such an approach, he adds, would take "a real mind-set change in management of breast cancer by doctors."

Minton acknowledges that researchers do not know what percentage of patients could be helped with preoperative drug treatment, since the currently accepted time periods between surgery and onset of chemotherapy may not be significant in slow-growing breast cancers. For some patients, however, neoadjuvant therapy "may be a truly significant factor," he says. In certain cases, Ragaz adds, the tumor cells can double in number within one to two months.



American College of Radiology

Studies show that the use of an X-ray technique called mammography can save lives through earlier detection of breast cancer. On the left is a normal mammogram, while the one on the right shows two cancerous growths.

Not only the timing of chemotherapy, but the timing of the surgery itself may be crucial to saving lives, says William J.M. Hrushesky of the University of Minnesota in Minneapolis. A chronobiologist, he studies the relationship between health and biological cycles, whether the rhythm of a heartbeat or that of the menstrual cycle. He reports that the ebb and flow of hormones during the fertility cycle of laboratory mice significantly affects their outcome following surgery for breast cancer – results that suggest it may be best to perform breast surgery in humans just before or during ovulation.

Because hormones affect the growth of breast cancer, Hrushesky and his coworkers hypothesized that the success of surgery was influenced by either the time during the cycle when the tumor began or the time it was surgically removed. One month after removing breast tumors from mice, the scientists looked for cancer in the animals' lungs. Of the 60 mice operated on during the fertile part of their cycle, 27 percent were disease-free, compared with 12.3 percent of the 73 treated while infertile – a two-fold improvement.

Hrushesky says it is difficult to extrapolate directly from the mouse cycle to that of humans, and human data need to be collected. "The duration of the window of opportunity is not clear [in humans]," he says. But he suggests, on the basis of his results, that the one-quarter to one-third of the menstrual cycle prior to ovulation "seems safe" for surgery. It is possible, he says, that the stress of surgery upsets the balance between cancer and normal cells to a greater extent at certain times. The Minnesota group also found that the body's natural killer cells – a defense against cancer – are most numerous during ovulation.

This may help explain why women with the same stage of breast cancer can respond so differently after surgery, says Benjamin F. Byrd of Vanderbilt Medical School in Nashville, Tenn. If subsequent studies reinforce the Minnesota findings, the concept will be adopted quickly by physicians, he predicts. Surgery could be scheduled during a specific time or hormones could be used to artificially create the optimal point in a woman's menstrual cycle. Hrushesky has attempted a retrospective study of surgery patients' charts, trying to correlate outcome with cycle timing. Unfortunately, he says, most physicians don't ask the key question of when a woman had her last period.

As with any research in its early stages, results from these studies may or may not evolve into standard clinical practices. Despite the increases in breast cancer expected among aging baby-boomers, however, researchers say they are optimistic – because such studies will eventually show us how to prevent death from breast cancer, if not how to prevent the disease itself. □