Drugs give slight edge in breast cancer

Women with breast cancer that has not spread to their lymph nodes have a slightly smaller risk of recurrence if given chemotherapy or hormonal treatment soon after surgery, according to four studies released last week. Treated women proved more likely than controls to remain cancer-free for as long as four years, but researchers say it's too early to detect any long-term survival advantage.

U.S. physicians will diagnose about 143,000 new breast cancers in 1989, according to the American Cancer Society. The new findings apply to a subset of about 70,000 women with node-negative breast cancer. "Although the prognosis of these women is generally considered positive, all too many of them will suffer recurrences," says Samuel Broder, director of the National Cancer Institute, which funded three of the studies reported in the Feb. 23 NEW ENGLAND JOURNAL OF MEDICINE.

Until recently, most women with node-negative breast cancer got primary treatment – either a mastectomy or surgical removal of the tumor plus radiation – but no chemotherapy. For 70 percent of node-negative patients that approach worked well, but the remainder went on to suffer cancer recurrence. The new research indicates routine use of adjuvant therapy might save an estimated 5,000 U.S. women each year from cancer recurrence and probable death. These are relatively modest results, however, and have triggered debate about whether doctors should prescribe drug therapy to all node-negative breast cancer patients.

In the first study, researchers in the National Surgical Adjuvant Breast and Bowel Project (NSABP) studied 679 node-negative patients, finding that women given chemotherapy – a combination of methotrexate and fluorouracil – had an 80 percent disease-free survival rate four years later, compared with 71 percent of controls. All study patients were at a higher risk of cancer recurrence because their tumors lacked estrogen receptors. Treatment patients got 12 four-week chemotherapy cycles and control patients got no adjuvant therapy.

Last May, after reviewing preliminary data from three of the four studies, the National Cancer Institute issued a clinical alert advising physicians to offer adjuvant therapy to women with node-negative breast cancer.

A second NSABP report involved 2,644 node-negative patients who had tumors with estrogen receptors – a type of breast cancer that often responds to hormone therapy. Treatment patients got tamoxifen, a synthetic hormone that blocks a tumor's ability to grow; control patients got placebo pills. Researchers found 83 percent of treatment patients disease-free after four years, compared with 77 percent of controls.

In the third report, Edward G. Mansour at the Cleveland Metropolitan General Hospital and his colleagues studied 406 node-negative women at high risk of cancer recurrence. Treatment patients got chemotherapy – cyclophosphamide, methotrexate, fluorouracil and prednisone – and controls received no additional therapy. After three years, 84 percent of the treatment patients and 69 percent of the controls were disease-free.

Finally, an international team of breast cancer researchers, the Ludwig Breast Cancer Study Group, published a study of 1,275 node-negative patients. Women in the treatment group got a brief course of chemotherapy – cyclophosphamide, methotrexate, fluorouracil and leucovorin – 36 hours after surgery and again a week later. Controls got no additional treatment. After four years, 77 percent of treatment patients were disease-free, compared with 73 percent of controls.

Comments William L. McGuire of the University of Texas Health Science Center in San Antonio, in an editorial accompanying the reports, "I would argue that the cost considerably outweighs the benefits of treating all node-negative patients, especially in the absence of a proved survival benefit." McGuire says mass treatment of all 70,000 node-negative cancer patients would mean 64,960 women would get unnecessary treatment each year at an estimated cost of $338 million. In addition, as many as 100 women would die as a result of the drug treatment, says McGuire. He suggests adjuvant treatment only for node-negative patients with a high risk of recurrence.

But doctors can't predict which node-negative patients will go on to suffer another bout with cancer, points out NSABP Project Chairman Bernard Fisher of the University of Pittsburgh. He recommends offering treatment to all node-negative breast cancer patients except those with microscopic tumors. "The 30 percent chance of a recurrence, with the inevitability of death due to metastases, is terrifying to most women," adds former National Cancer Institute Director Vincent T. DeVita Jr., now at Memorial Sloan-Kettering Cancer Center in New York City. He calls the risk of death from drug therapy "minuscule by comparison."

The American Cancer Society says the decision to go ahead with drug therapy should be an individual one, based on a doctor's recommendation.

– K.A. Fackelmann

Plant ion-pump gene cloned, sequenced

Scientists for the first time have cloned and sequenced a gene for an energy-generating protein that controls a higher plant's ability to take up nutrients from soil. The research might someday allow plant breeders to genetically engineer crops that more efficiently extract essential minerals through their roots, says molecular biologist and study leader Michael R. Sussman at the University of Wisconsin-Madison.

Better nutrient-extracting crops could live in deficient soils and so need little or no added fertilizer, reducing a farmer's costs and decreasing pollution from fertilizer runoff. By isolating "the gene for this very important function that is common to all plants, [Sussman] has found a tool by which we can study one of the fundamental processes [in plant growth]," says University of Wisconsin-Madison horticulturist Warren H. Gabelman.

The gene codes for a protein that crosses the outer membrane of all plant and fungal cells and transports hydrogen ions from one side of the membrane to the other. The pump creates an electrical difference between a cell's inside and outside, producing "the most electricity of any protein in nature," Sussman says. A root cell uses this electricity to bring in soil nutrients.

Sussman and co-workers Jeffrey F. Harper and Terry K. Surowy wanted to study the gene for the pump from a plant of the mustard family, *Arabidopsis thaliana*, because of this plant's short lifespan and small number of genes. They used what they knew about the protein structure of an oat plant's pump to create a short genetic probe that pinpointed a partial-length oat gene. They then used this oat gene to find an equivalent full-length gene in *A. thaliana*, they report in the February PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES (Vol.86, No.4).

Although researchers identified the pump gene in fungal DNA several years ago, it has proved more difficult to pick out in higher plants because the protein exists in tiny amounts.

Sussman and his research team are now trying to insert the newly identified gene into tobacco plants in a way that will cause the plants to produce an abnormally large number of proton pumps. "If we can [do this] without hurting the plant, we may be able to improve nutrient uptake [in all kinds of plants]," Sussman says. They also hope to use the gene to find its counterparts in many agricultural crops to correlate genetic variations to variations in nutrient-absorbing ability, Sussman says.

– I. Wickelgren