

# The Adjuvant Advantage

*Breast cancer therapies promise a longer life*

By KATHY A. FACKELMANN

Cancer researchers are turning to a statistical compass of sorts in their search for a cure for breast cancer: not just prolonging life a few more years, but an out-and-out cure.

A powerful statistical technique called meta-analysis now confirms that adjuvant therapy, additional treatment provided after breast cancer surgery, can improve survival among women with early stages of breast cancer. A second study suggests that an experimental drug extracted from the bark of the rare Pacific yew tree may one day yield even greater gains against this scourge.

According to the American Cancer Society, one in nine American women will develop breast cancer at some point in her life. This year alone, physicians will diagnose an estimated 180,000 new cases of breast cancer in the United States and the disease will kill approximately 46,000 women and 300 men. Furthermore, a December 1991 General Accounting Office report on breast cancer notes an alarming rise in the number of new cases reported each year, an increase scientists can't fully explain.

When a woman learns she has a lump in her breast, her doctor generally recommends a biopsy, the removal of suspicious tissue from the breast. If the examination shows malignant tissue, the woman often gets a primary treatment of surgery, radiation or both.

Like other cancers, breast cancer occurs when cells lose their normal growth-control mechanism and begin to divide wildly and aggressively. In early stages of the disease, surgeons can usually remove all detectable cancer in the breast and the nearby lymph nodes. However, cancer often proves devious: Oncologists estimate that a tumor the size of a pinhead contains about a million cancer cells. If some of those cells make their way into the bloodstream, the disease can spread, or metastasize, and spring to life months or years later in the bone, liver or other parts of the body. Such widespread cancer is very difficult to treat and is nearly always fatal.

To lessen the threat of metastasis, oncologists often suggest that women with early breast cancer get a variety of adjuvant treatments, including chemotherapy and hormonal therapy. Chemotherapeutic drugs, such as doxorubicin, kill cancer cells, while the milder hormonal drugs, such as tamoxifen, block the cancer cells' out-of-control growth.

In May 1988, the National Cancer Institute (NCI) issued a clinical alert advising doctors to consider adjuvant therapy for women with early breast cancer. Then the Feb. 23, 1989 *NEW ENGLAND JOURNAL OF MEDICINE* published four studies indicating that women with early breast cancer who get adjuvant therapy are more likely than controls to remain cancer-free for four years (SN: 3/4/89, p.135). Preliminary data from three of these four studies had provided the impetus for NCI's clinical alert.

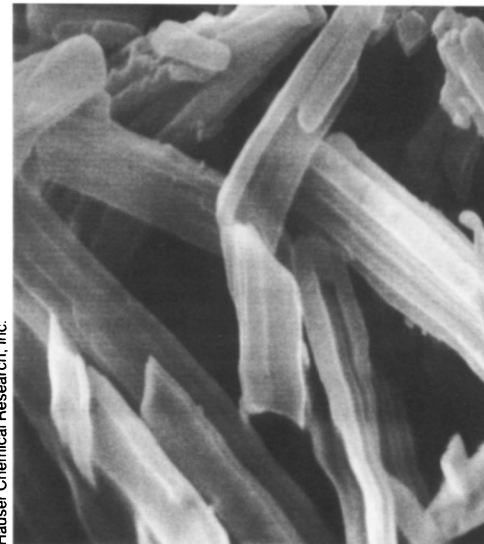
Some physicians remained skeptical of adjuvant therapy's worth, however, noting that the 1989 studies had failed to prove that such treatment improves a woman's chance of long-term survival. They also pointed out that women paid dearly for the few cancer-free years they gained. For example, chemotherapy often triggers hair loss, vomiting, nausea and other side effects. Hormonal therapy can cause symptoms of menopause, such as hot flashes.

While providing no guarantees, a new study detailed in the Jan. 4 and Jan. 11 issues of *LANCET* adds compelling survival statistics to the mix of costs and benefits offered by adjuvant therapy. Statistician Richard Peto, director of the Cancer Studies Unit at England's Oxford University, and an international team of collaborators culled data from 133 randomized breast cancer trials involving a total of 75,000 women worldwide who had received a variety of postsurgical treatments, including hormonal therapy and chemotherapy.

The data revealed that women with early breast cancer who opt for chemotherapy or hormonal treatment had improved their odds of surviving. According to the American Cancer Society, about 60 percent of U.S. breast cancer cases are considered early breast cancer, in which the malignancy is in the breast alone (Stage I) or in the breast and nearby lymph nodes (Stage II).

The team found that each year, women who got the drug tamoxifen after surgery showed a 25 percent reduction in the risk of cancer recurrence and a 17 percent lessening in the overall risk of death.

(Statisticians consider overall death rates a more significant marker of treatment success than mortality due to breast cancer alone, says Richard Gray of Oxford University, a coauthor of the report. If researchers analyzed breast cancer rates alone, they could miss treatment-



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related side effects that emerge as a surge in the overall death rate, he says.)

Similar results surfaced when the team looked at the data from the chemotherapy trials. Each year, women who received chemotherapy had a 28 percent reduction in their risk of another bout with breast cancer and a 16 percent decrease in their chances of dying.

The year-by-year statistics appeared encouraging, but would they hold up in the long run? Most women receive chemotherapy or tamoxifen therapy for six months to several years after surgery. Many researchers, including those who participated in this study, believed that any advantage to adjuvant therapy would accrue during the first five years after surgery.

"What was really surprising was that from year 5 to 10 the size of the benefit doubled," Gray told *SCIENCE NEWS*. He recalls that at a meeting held to unveil the data, the 10-year survival statistics elicited a collective gasp from the collaborators. "We didn't think the [benefit] would be as dramatic as it was," adds I. Craig Henderson, a U.S. collaborator who is at the Dana-Farber Cancer Institute in Boston.

Oncologists know that many women with early breast cancer will face no additional bout with cancer after their primary treatment of surgery and/or radiation. The new data show that additional therapy with chemotherapy or hormonal drugs produced 12 extra 10-year survivors for every 100 women treated with Stage II breast cancer. The benefit was smaller for women with Stage I breast cancer: Adjuvant therapy produced 12 extra 10-year survivors for every 200 women treated.

"You suddenly start getting quite a substantial benefit of adjuvant treatment," Gray says. The *LANCET* data suggest that such therapy would save an estimated 10,000 women each year worldwide, he adds.

For most women, the data detailed in the *LANCET* offer compelling evidence of



*Pure taxol crystals as seen through a scanning electron microscope. To get the crystalline form, chemists must work with a crude extract taken from the bark of a yew tree.*

adjuvant therapy's advantage, says F. Andrew Dorr of the National Cancer Institute.

However, Henderson still believes that some women do not need any treatment after their surgery. For example, women with very tiny tumors have little chance of metastasis after surgery, and additional therapy will not change their prognosis much, he says.

**W**hile the study's results offer a valuable overview of adjuvant therapy, they also reveal some intriguing bits of information for specific population groups. For example, for women age 50 and younger, ovarian ablation — the destruction or removal of the ovaries by radiation or surgery — proved just as effective as chemotherapy. Estrogen, the sex hormone produced by the ovaries, can fuel the growth of some breast tumors, and ablation may prevent the recurrence of such malignancies by reducing concentrations of estrogen in the bloodstream, Gray explains.

An editorial in the Jan. 11 LANCET urges cancer specialists to reexamine ovarian ablation in light of the new findings. This method of cancer treatment fell out of favor during the 1970s, especially in the United States, where oncologists favor chemotherapy. Dorr remains cautious about the ablation approach, however, noting that meta-analysis offers an incomplete picture of its value.

For older women with breast cancer, meta-analysis yields some particularly surprising and important findings. For women age 50 and older, the drug tamoxifen helped stave off the spread of cancer, even if their tumor cells lacked detectable estrogen receptors. Tamoxifen was thought to prevent metastasis by binding with a tumor's estrogen receptor. Once bound to the receptor, tamoxifen stopped estrogen from delivering its growth message to the tumor cell — or so the theory went.

How does tamoxifen work when tumors lack these crucial receptors? Nobody really knows yet, Gray admits.

**A**s researchers mull over the implications of the report in LANCET, a scientific team from Texas is taking the next step in the arduous journey toward a truly effective treatment. The team's data suggest that an experimental drug called taxol may help women beat the breast cancer odds.

The taxol story starts with a look at the past: Native Americans in the Pacific Northwest used the bark of the Pacific yew (*Taxus brevifolia*) to protect them from lightning. Taxol hasn't demonstrated its anti-lightning properties recently, but in the 1970s researchers discovered that it possessed a powerful ability to suppress tumors — at least in the test tube.

Then, in 1988, a scientific team at Johns Hopkins University in Baltimore showed



*To protect the rare Pacific yew, scientists are trying to find alternative ways of producing taxol. In the future, chemists may extract this potentially lifesaving compound from the tree's needles rather than the bark.*

that taxol provided some benefits to women with severe ovarian cancer. Now, a team led by Frankie A. Holmes of the M.D. Anderson Cancer Center in Houston suggests the drug may help women with breast cancer as well.

Holmes and her colleagues studied 25 women with advanced breast cancer who had failed to respond to chemotherapy. The women received a 24-hour infusion of taxol once every 21 days. After an average of nine months in the study, 56 percent of the women experienced some tumor shrinkage, the team reports in the Dec. 18 JOURNAL OF THE NATIONAL CANCER INSTITUTE.

Three of the women (12 percent) went into complete remission after getting this drug for up to 15 months. Complete remission means the women showed no evidence of malignancy after their treatment, notes coauthor Richard L. Theriault, also at M.D. Anderson. Cancer has since recurred in two of the three women, he adds. Side effects reported in this study included muscle aches similar to those that accompany the flu, as well as an inhibition of white blood cells, a problem that could increase vulnerability to infection, Theriault says.

The study, although preliminary, gives research scientists hope that taxol will provide more firepower in the battle against breast cancer. "I think it's very encouraging," Eric K. Rowinsky of the Johns Hopkins Oncology Center told Sci-

ENCE NEWS. "The best [available] drug in breast cancer produces response rates ranging from 35 to 45 percent," he adds.

While the women in the Texas trial all had severe disease, Rowinsky and others hope that taxol's prowess will extend to women with early breast cancer as well. "Our ultimate goal is to incorporate taxol into basic therapy," he says.

How does the drug work? In 1979, Peter B. Schiff, then a graduate student at Albert Einstein Medical College in New York City, discovered that taxol interfered with microtubules, small hollow tubes in the cell that play a role in cell division. Poisoning the microtubules prevents the cancer cell from dividing, he notes.

Schiff, now at Columbia University's College of Physicians and Surgeons in New York City, says his current research

hints that taxol combined with radiation may deliver a double whammy to dividing cancer cells, a strategy he plans to test in a trial of breast cancer patients. M.D. Anderson's team has embarked on another strategy: They are combining taxol with other, proven anticancer drugs in an attempt to synergistically blast breast cancer cells.

If such double-duty treatments help women with advanced breast cancer, oncologists will begin treating those with early breast cancer, Schiff notes.

**W**hile a cure remains the ultimate goal of such research, Henderson cautions against unbridled optimism. Breast cancer remains a formidable foe, he says, noting that some people can suffer a recurrence 30 years after their initial bout with the disease.

The LANCET data suggest that breast cancer patients who receive treatment after surgery can increase their chances of living at least a decade. Longevity may further improve with taxol in the doctor's bag. While adjuvant therapy may not kill every last cancer cell lurking in the body, it does give the body's own immune system an edge in the battle. Adjuvant therapies can and do prolong life, Henderson says: "When you start living a couple of decades longer, then cure versus prolongation of life becomes semantic." □