



Researchers Focus On Hormone-Negative Breast Cancer

BY ELIZABETH WHITTINGTON

When Cindy Coleman went for a biopsy after feeling a lump during a self breast exam in 2002, she went straight to the computer to learn as much as she could before her next doctor's appointment. When the doctor told her that her cancer was negative for both estrogen receptors and the overexpression of the HER2 gene, she already understood what it meant—the targeted agents that had been publicized in the news did nothing for her cancer.

“I can tell you that every time I heard of or read of an announcement of some new medication that was promising for women with breast cancer, only to read or hear further that it was for women whose cancer is hormone driven, my heart would sink and break into a million pieces,” says Coleman.

A World of Difference

When a woman is diagnosed with breast cancer, the pathology report lists the tumor's hormone receptor status—does the surface of the cancer cells have receptors for estrogen on them? Estrogen receptor-positive breast cancer may be treated with hormone therapy that specifically targets estrogen receptors because it distinguishes them from normal cells. Hormone treatments, such as tamoxifen or an aromatase inhibitor, taken for five years will further prevent the disease from recurring.

But for about a third of breast cancer patients, the pathology report will come back with a diagnosis of ER-negative breast cancer. Although the proportion of postmenopausal women with estrogen receptor-negative cancers is actually quite small, premenopausal women make up a somewhat larger percentage of patients with hormone receptor-negative cancers that are insensitive to hormone therapy. Other population groups that have a disproportionate number of ER-negative cancers are women of African descent, especially those who are young, and women who test positive for the BRCA1 mutation.

New Research, New Treatments

“We feel ignored by the scientific community,” says Coleman, who has since created a website for other breast cancer survivors called www.truefacesofbreastcancer.org. “I would think that the mystery of what is

driving hormone receptor-negative cancer would really challenge them enough to look more into it.”

Solving that mystery is why researchers from leading cancer institutes, including Dana-Farber Cancer Institute in Boston, are pouring funds and energy into uncovering the cause of ER-negative cancers through the Center for Research on the Prevention and Treatment of ER-Negative Breast Cancer. The four-year study, which began in 2003, has aimed to divide efforts into six major research projects, including finding new targets that are present in high levels on the surface of ER-negative cancer cells, including growth factor receptors.

Other research that has been gaining ground is testing different combinations of chemotherapy. A study published in the *Journal of American Medical Association* last year showed a newer chemotherapy combination of biweekly Adriamycin® (doxorubicin) and Cytosan® (cyclophosphamide) plus Taxol® (paclitaxel) lowered the rate of recurrence and death in women with hormone receptor-negative breast cancer by more than 50 percent compared with the older low-dose combination of Cytosan, Adriamycin and fluorouracil.

Balancing the Positive with the Negative

Although both estrogen and progesterone are examined during pathology, doctors pay more attention to the estrogen receptor when determining hormone receptor status. “To a large extent, when (hormone status is) mixed, we still consider the tumor hormonally sensitive,” says Eric Winer, MD, director of the Breast Oncology Center at Dana-Farber.

At least 10 percent of breast cancers are ER-positive and progesterone receptor negative, and many experts believe these so-called mixed cancers are less sensitive to hormone therapies than when both hormone receptors are present. Cancers that are ER-negative but PR-positive are very rare, making up about 5 percent of breast cancer cases, and may respond to hormone therapy because progesterone is thought to be important in aiding estrogen receptor function and possible cancer cell growth.

Determining hormone status is not the only factor that guides treatment options. “There are subtypes, including those that are more or less hormone negative, but HER2-positive, which is a protein that drugs such as Herceptin and lapatinib target,” says Lisa Carey, MD, medical director of the Breast Center at UNC Lineberger Comprehensive Cancer Center in Chapel Hill, North Carolina.

Herceptin® (trastuzumab) is a monoclonal antibody that acts against the HER2 protein overexpressed in some cancers. It is approved for both early-stage and metastatic HER2-positive breast cancer. Tykerb® (lapatinib) is an investigational drug for advanced breast cancer that targets both HER2 and HER1 (also called epidermal growth factor receptor 1). Tykerb is expected to be approved early this year.

Scientists are also examining breast tumors for the presence or absence of androgen receptors since recent studies show androgens inhibit the growth of some breast cancer cells. A study is under way to determine if Androxy®, a synthetic androgen hormone, plus the aromatase inhibitor, Arimidex®

(anastrozole), can inhibit the production of estrogen. Investigators hope the combination of these two drugs will inhibit tumor growth and shrink them before surgery.

Preventing Recurrence

Since women with ER-negative tumors do not benefit from drugs that act on estrogen, researchers must discover what fuels estrogen-negative cancer in order to inhibit cancer growth.

In postmenopausal women, the ovaries no longer release estrogen, but fat cells—although to a much lesser degree when compared with the ovaries—continue to release the hormone after menopause. Interim results of the Women’s Intervention Nutrition Study published in 2006 in the *Journal of the National Cancer Institute* examined if a low-fat diet (defined as having 15 percent of calories or less come from fat intake) affected breast cancer recurrence. Experts expected postmenopausal women with a history of estrogen-fueled cancers to lower their risk of recurrence if they consumed less fat. Surprisingly, while experts expected the ER-positive group to have a lower risk of recurrence, it was the ER-negative group that most benefited from the diet change. Women with a history of ER-negative disease saw a median risk reduction of 42 percent compared with 15 percent in women with ER-positive disease. Final results of the study are still pending.

“That was a hypothesis we had going in that (risk) would be mediated by estrogen change, but it looked like a potentially larger effect was in the receptor-negative group,” said Rowan Chlebowski, MD, PhD, lead author of the study, in a previous *CUI CURE* interview. “Something other than estrogen was likely mediating that change.”

Although Coleman says she is happy not to have had to take tamoxifen, which carries a small risk of cataracts and endometrial cancer (cancer in the lining of the uterus), she is concerned that women with hormone-receptor negative breast cancer do not get necessary attention from the scientific community. Hopefully with the current research for this type of breast cancer, she will soon have more to read about.