

# CANCER ADVANCES IN FOCUS

## Breast Cancer

### Thirty-Five Years Ago

- Approximately 75% of women diagnosed with breast cancer survived their disease at least 5 years.
- Mastectomy was the only accepted surgical option for breast cancer treatment.
- Only one randomized trial of mammography for breast cancer screening had been conducted.
- Clinical investigation of combination chemotherapy, using multiple drugs with different mechanisms of action, and of hormonal therapy as post-surgical (adjuvant) treatment for breast cancer was in its earliest stages.
- Hormonal treatment of inoperable or advanced breast cancer with tamoxifen, a selective estrogen receptor modulator (SERM), was being investigated but had not yet been approved by the U.S. Food and Drug Administration (FDA).
- Genes associated with an increased risk of breast cancer had not yet been identified.
- Hormonal therapy with SERMs, such as tamoxifen, and aromatase inhibitors is now standard in the treatment of women with estrogen receptor-positive breast cancer, both as adjuvant therapy and in the treatment of advanced disease. Estrogen receptor-positive breast cancer cells can be stimulated to grow by the hormone estrogen. SERMs interfere with this growth stimulation by preventing estrogen from binding to its receptor. In contrast, aromatase inhibitors block estrogen production by the body. FDA-approved aromatase inhibitors include anastrozole, exemestane, and letrozole.
- Tamoxifen and another SERM, raloxifene, have been shown in clinical trials to prevent the development of invasive breast cancer in women at high risk of this disease. Tamoxifen has already been approved by the FDA as a breast cancer prevention drug.
- The monoclonal antibody trastuzumab is being used to treat breast cancers that overproduce a protein called human epidermal growth factor receptor 2 or HER2. This protein is overproduced in about 20% of breast cancers. These HER2-overproducing cancers tend to be more aggressive and are more likely to recur. Trastuzumab targets the HER2 protein, and this antibody, in conjunction with adjuvant chemotherapy, can lower the risk of HER2-overproducing breast cancer recurrence by 50% compared to chemotherapy alone.
- The study of large groups of related individuals (kindreds) has led to the identification of several breast cancer susceptibility genes, including *BRCA1*, *BRCA2*, *TP53*, and *PTEN/MMAC1*. Mutations in *BRCA1* and *BRCA2* account for approximately 80-90% of all hereditary breast cancers, and women who carry mutations in these genes have a lifetime risk of breast cancer that is roughly 10 times greater than that of the general population.

### Today

- Nearly 90% of women diagnosed with breast cancer will survive their disease at least 5 years.
- Breast-conserving surgery (lumpectomy) followed by local radiation therapy has replaced mastectomy as the preferred surgical approach for treating women with early stage breast cancer.
- Routine mammographic screening is an accepted standard for the early detection of breast cancer. The results of eight randomized trials and of the NCI-ACS Breast Cancer Detection Demonstration Projects established that mammographic screening can reduce mortality from breast cancer.
- Combination chemotherapy has become standard in the adjuvant treatment of women with early stage breast cancer. The goal of this systemic therapy is to eradicate cancer cells that may have spread beyond the breast. Neoadjuvant chemotherapy, or chemotherapy given before surgery to reduce the size of the tumor and to increase the chance of breast-conserving surgery, is being studied in clinical trials.

## Tomorrow

We will exploit our rapidly increasing knowledge of genetics, molecular biology, and immunology to develop even more effective and less toxic treatments for breast cancer. We will expand our ability to target and disrupt the effects of molecular changes that cause breast cells to become cancerous. In addition, we will use this knowledge to personalize breast cancer therapy. For example:

- Gene expression analysis has led to the identification of five subtypes of breast cancer that have distinct biological features, clinical outcomes, and responses to chemotherapy. This knowledge should allow the development of treatment strategies based on an individual's tumor characteristics.
- A patient's response to chemotherapy is influenced not only by the tumor's genetic characteristics but also by inherited variation in genes that affect a person's ability to absorb, metabolize, and eliminate drugs. This knowledge should allow prediction of tumor response to and the likelihood of severe adverse effects from individual chemotherapy drugs or classes of drugs. It should also aid in the design of more effective and less toxic chemotherapeutic agents.