

# BREAST CANCER UPDATE

## GENETICS, SURGERY, AND RADIATION THERAPY

### BRCA Genetic Testing: Implications for the Surgical Oncologist

“BRCA gene mutation testing is the only way to identify specific individuals in a family who are at risk for breast cancer,” said David M. Euhus, Associate Professor of Surgery, University of Texas Southwestern Medical Center, Dallas. He discussed patient management issues for women who have a positive BRCA gene test, including those with and without breast cancer.

Dr. Euhus presented the case of a 40-year-old woman whose sister had breast cancer at age 42 and whose mother had bilateral breast cancer at ages 40 and 44. The woman’s grandmother had ovarian cancer. Because “inherited predisposition syndromes are autosomal dominant, meaning only half of the individuals in any generation will have the detrimental gene, it’s a 50/50 toss-up as to whether this patient is at high risk or not,” said Dr. Euhus.

The patient was found to have the BRCA1 mutation, which meant she had a 66% chance of developing breast cancer in her lifetime and a 32% chance of developing ovarian cancer. Without the BRCA mutation, her risk would be comparable to the general population.

“Managing this patient involves striking a balance between maximal risk reduction and the patient’s preferences concerning intervention options,” said Dr. Euhus. He added that there are no inherently bad choices, as long as the decisions are well informed. The options for managing risk in patients with a BRCA mutation include surveillance, chemoprevention, and prophylactic surgery.

The Cancer Genetic Studies consortium suggests that women with BRCA1 or 2 gene mutations should begin breast self-examination at age

*Improving breast cancer survival involves early detection and a range of modalities, including surgery, radiation, systemic chemotherapy, and hormonal therapies. At a symposium held March 6, 2003, during the Annual Meeting of the Society of Surgical Oncology, four experts discussed BRCA gene testing, breast conservation surgery, aromatase inhibitors for early breast disease, and accelerated radiation therapy.*

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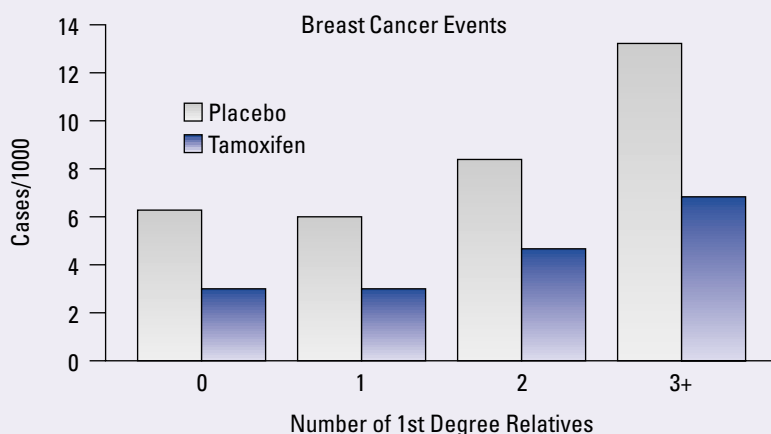
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**Figure 1. Tamoxifen in Women with High Risk Family Histories**



Source: *J Natl Cancer Inst.* 1998;90:1371-1388.

18, and at age 25 they should have breast examinations by a physician every 6 or 12 months and begin annual mammograms. “A good rule of thumb,” said Dr. Euhus, “is to begin screening mammography 10 years before the earliest breast cancer diagnosis in the family.”

**“Tamoxifen reduced the breast cancer rate, regardless of the number of first-degree relatives with breast cancer,” said Dr. Euhus.**

Studies have shown that BRCA gene mutation carriers have higher breast density than non-carriers, making detection of breast cancer on mammograms difficult. Dr. Euhus mentioned three studies that compared mammograms to breast MRIs, and showed that “of 100 women with BRCA mutations and normal mammograms, three breast cancers will be detected by MRI” (*Br Cancer Res Treat.* 2000;63:53; *J Natl Cancer Inst.* 2001;93:1095; *J Clin Oncol.* 2001;19:3524). The downsides of MRI are the expense and the false-positive rate of 6%.

On the topic of chemoprevention, Dr. Euhus discussed the tamoxifen study, in which 13,388 at-risk women were randomized to tamoxifen or

placebo (*J Natl Cancer Inst.* 1998;90:1371-1388). The women were divided into groups according to degree of risk, which was calculated by the number of first-degree relatives with breast cancer: three, two, one, and none. “Tamoxifen reduced the breast cancer rate, regardless of the number of first-degree relatives with breast cancer,” said Dr. Euhus. (Figure 1)

In a further analysis of women with strong histories of breast cancer, Mary Claire King, MD, found that tamoxifen did not reduce risk for breast cancer in women with BRCA1 gene mutations. “This makes sense because 80% of the breast cancers that grow in BRCA1 gene mutation carriers are estrogen-receptor negative,” said Dr. Euhus.

Tamoxifen only reduces risk of estrogen-receptor positive breast cancer; most BRCA2 mutation-associated cancers are estrogen-receptor positive. In Dr. King’s analysis, there was a 50% reduction in BRCA 2-associated cancers in women taking tamoxifen.

The third option for BRCA1 and 2 carriers is prophylactic surgery, with oophorectomy generally being the most acceptable to women who are not concerned about having children. Dr. Euhus cited a study which found a 50% reduction in risk of breast cancer in premenopausal women who have their ovaries removed (*N Engl J Med.* 2002;346:1616).

Prophylactic mastectomy is a “very effective way to reduce the risk of breast cancer,” continued Dr. Euhus. He noted that nipple-sparing subcu-

taneous mastectomy can be done, but breast cancer can still occur after this surgery. “I have not found a case of breast cancer after a good oncologic total mastectomy,” he said.

He emphasized that to avoid feelings of regret in the patient, she must be well informed and she should make the decision, rather than being talked into it by her physician.

Dr. Euhus turned to the topic of managing patients with BRCA gene mutations who have breast cancer. While removing both breasts will “pretty much resolve the issue,” he said, some women prefer a less radical approach. For these women the questions are: Is ipsilateral breast tumor recurrence rate going to be acceptable following lumpectomy and radiation? And, what’s the risk of contralateral second primary breast cancer?

There’s no evidence of improved survival with mastectomy compared to breast conservation. However, Dr. Euhus noted that some recently published studies have found a higher local recurrence rate in BRCA gene mutation carriers who’ve undergone lumpectomy compared to women with sporadic breast cancers who’ve had lumpectomy.

He presented data showing that BRCA mutations are associated with increased risk of ipsilateral and second primary breast cancers, and survival may be worse for BRCA gene mutation carriers. “But, overall, lumpectomy with whole breast radiation is still considered an acceptable option,” he said. ■

## How the NSABP B-04 and B-06 Trials Relate to Current Breast Cancer Management: A Personal Perspective

In 1971, Bernard Fisher, MD, participated in the National Surgical Adjuvant Breast and Bowel Project (NSABP) study B-04, which sought to determine whether less radical surgery for breast cancer was as effective as the Halsted radical mastectomy. In 1976, he compared lumpectomy to total mastectomy, in a study called NSABP B-06.

In 2002, Dr. Fisher, Distinguished Service Professor, University of Pittsburgh and Scientific Director, National Surgical Adjuvant Breast and Bowel Project, published 25- and 20-year, respectively, results from these two studies (*N Engl J Med.* 2002;347:567-575; *N Engl J Med.* 2002; 347:1233-1241). He discussed these findings.

In the late 1960s, Dr. Fisher proposed a controversial hypothesis that contradicted some common views held at the time. His hypothesis included the beliefs that breast cancer is often a systemic disease, tumor cells may be disseminated by the time of diagnosis, and variations in effective local therapy are unlikely to have a major

**Dr. Fisher noted that since the B-06 trial, use of systemic therapy has markedly reduced the rate of ipsilateral breast tumor recurrence.**

effect on survival.

In 1971, Dr. Fisher tested some of his hypotheses in the B-04 study, which included 1,079 women with negative axillary nodes who underwent radical mastectomy, total mastectomy without axillary dissection but with postoperative irradiation, or total mastectomy plus axillary dissection only if their nodes became positive. There were also 586 women with positive

axillary nodes who had either radical mastectomy or total mastectomy without axillary dissection but with postoperative irradiation.

Dr. Fisher was criticized at the time by some breast cancer experts who believed the less radical surgeries were inferior. However, early findings showed no significant differences between the groups with respect to disease-free survival, relapse-free survival, distant-disease-free survival, or overall survival. These findings remained the same 25 years later.

“Despite this, many issues remained,” said Dr. Fisher, such as the extent of breast removal that is needed. “More extensive surgery has merits for local disease control, but there was no increase in distant disease or breast cancer mortality from less extensive surgery,” he said.

Another question: Are recurrences or survival rates influenced by the number of nodes removed? In 1981, Dr. Fisher reported that “limited axillary dissection with removal of relatively

few nodes is adequate to determine whether a patient has negative or positive axillary nodes.”

Yet another question he raised is, “Does radiation improve the survival of women with operable breast cancer?” His findings suggest that if radiation therapy improves survival, it is only by a small amount.

In summary, “the B-04 study provided evidence for abandoning cancer surgery based on Halstedian principles and freed us from the shackles of those concepts,” said Dr. Fisher.

In 1976, Dr. Fisher conducted the B-06 trial. In that study, 1,851 women were randomly

assigned to total mastectomy, lumpectomy alone, or lumpectomy and breast irradiation. At 20 years, 40% of women who underwent lumpectomy alone had ipsilateral breast tumor recurrence, compared to 15% of those who received lumpectomy plus radiation. However, in terms of disease-free survival, distant-disease-free survival, and overall survival, there were no differences in outcome among the three groups.

Dr. Fisher noted that since the B-06 trial, use of systemic therapy has markedly reduced the rate of ipsilateral breast tumor recurrence.

He next addressed the question of whether

postoperative breast irradiation is necessary. His work has shown that for tumors of 1 cm or less, tamoxifen is effective in controlling ipsilateral breast tumor recurrence, radiation is more effective, and the combination of both therapies is the best.

He concluded with a discussion of systemic therapy in combination with surgery, noting that for large tumors preoperative chemotherapy should be used to reduce tumor size so that lumpectomy can replace mastectomy.

“In my view, mastectomy should no longer be considered a primary treatment for most patients with breast cancer,” he concluded. ■

## Impact of Aromatase Inhibitors in Early Breast Cancer

**M**ichael Baum, MD, Professor Emeritus of Surgery and Visiting Professor of Medical Humanities, University College of London, discussed the impact of aromatase inhibitors in the adjuvant therapy of early breast cancer.

Recently, scientists have achieved a greater understanding of the mechanism by which androgens from the adrenal gland are metabolized to estrogens via the aromatase enzyme in the peripheral tissues. First-generation aromatase inhibitors acted high up in the metabolic pathway and were, therefore, highly toxic. The more selective third-generation aromatase inhibitors act further down, interfering with the biosynthesis of testosterone to estradiol or androstenedione to estrone and then to estradiol. Therefore, these drugs are specific, non-toxic, and well tolerated.

Three of these agents are currently available: anastrozole and letrozole, which are non-steroidal, and the steroidal exemestane.

“Some clinical trials have shown that for hormone-receptor-positive advanced breast cancer, the aromatase inhibitors are superior to megestrol acetate in second-line therapy,” said Dr. Baum. There’s no cross resistance with tamoxifen and there’s better tolerability and efficacy than tamoxifen in first-line therapy, he added.

Dr. Baum described the Anastrozole Tamoxifen Alone or in Combination (ATAC) trial, which includes over 9,000 postmenopausal women with breast cancer who had completed primary therapy (*Lancet* 2002;359:2131). They were randomly assigned to receive anastrozole, tamoxifen, or a combination of both drugs for 5 years. About 84% of the patients were hormone receptor positive.

The study is still ongoing, so data on distant disease-free survival and overall survival are not yet available. However, at a median follow-up of 4 years data are available on disease-free survival, safety, and tolerability.

Dr. Baum pointed out that at 42 months, the combination arm of the trial was closed because the statisticians determined that “it is significantly

unlikely that the combination arm would ever do better than tamoxifen alone.” Therefore, the analyses are a direct comparison of tamoxifen and anastrozole.

Out of over 3,000 patients in each arm, there were 413 events in the anastrozole arm and 472 in the tamoxifen arm. Events were local, regional, or distant recurrence or contralateral disease (Table 1). “In absolute terms, there was a difference favoring anastrozole of 2.4% in the overall population,” said Dr. Baum. For hormone-receptor-positive patients, the hazard ratio was 0.82, which is a relative risk reduction of 18%, translating into a 2.9% absolute difference, which is both clinically and statistically significant, he added.

In a subgroup analysis of patients with a poor prognosis who were given chemotherapy up front, Dr. Baum noted a strong effect favoring anastrozole over tamoxifen in the chemotherapy-naive group but an equivalent effect between anastrozole and tamoxifen among those who received chemotherapy. “From this subgroup analysis, we can say that anastrozole and tamox-

ifen are equally effective in the presence of chemotherapy,” he said.

In terms of toxicity and tolerability, there were fewer hot flushes with anastrozole than tamoxifen, but it still occurred in about one-third of patients. Anastrozole also caused less vaginal discharge and bleeding than tamoxifen. Other advantages include reduction in ischemic cerebrovascular events and venous thromboembolic events. On the other hand, tamoxifen patients had fewer fractures, probably due to the demineralization effect of anastrozole.

Both drugs were well tolerated; 5.6% of women in the anastrozole arm and 8% of women in the tamoxifen arm withdrew because of drug-related adverse events.

“Anastrozole should be considered a choice for the treatment of postmenopausal women with hormone-sensitive early breast cancer,” Dr. Baum concluded. He cautioned that bone mineral density should be monitored and that anastrozole is probably contraindicated in women with osteopenia or osteoporosis. ■

**Table 1. First Events in Overall Populations**

	Anastrozole n = 3125 (%)	Tamoxifen n = 3116 (%)
First event	413 (13.2)	472 (15.1)
Locoregional recurrence	84 (2.7)	101 (3.2)
Distant recurrence*	196 (6.3)	223 (7.2)
Contralateral (invasive)	20 (0.6)	35 (1.1)
Contralateral (DCIS)	5 (0.2)	5 (0.2)
Death (non-breast cancer)	108 (3.5)	108 (3.5)

\*Including deaths from breast cancer, in absence of prior information about recurrence  
Source: *Lancet* 2002;359:2131.

## Advances in Accelerated Radiation Therapy

**D**ouglas Arthur, MD, Clinical Director of Radiation Oncology at the Virginia Commonwealth University, Medical College of Virginia Campus, discussed accelerated partial breast irradiation following lumpectomy.

“Accelerated partial breast irradiation involves delivery of radiation therapy to the lumpectomy cavity (plus a 1 to 2 cm margin) after conservative surgery using brachytherapy techniques,” said Dr. Arthur. The treatment is completed in 4 to 5 days as opposed to the conventional whole breast treatment that requires 6 to 7 weeks.

This procedure has the potential to increase the use of a breast preserving treatment approach, which is underutilized because of the time and distance barriers that accompany a conventional 6-week course of radiation. The procedure also has the possibility of reducing acute and chronic toxicity compared to external beam radiotherapy, thereby improving quality of life, according to Dr. Arthur.

The scientific rationale grows out of the fact that 80% to 90% of recurrences after breast conserving therapy occur in the tumor bed region, and therefore the target, historically believed to be the whole breast, appears to be the lumpectomy site plus a 1 to 2 cm margin. Therefore, whole breast radiotherapy may not

be needed in selected early stage patients.

Dr. Arthur presented data showing that recurrences away from the tumor bed (“elsewhere” failures) are rare after lumpectomy alone and following whole breast radiotherapy, which raises the question of whether whole breast radiotherapy is doing anything for disease outside the area of lumpectomy.

### Whole breast radiotherapy may not be needed in selected early stage patients.

Several institutions are actively involved in testing the approach of partial irradiation, and Dr. Arthur presented a compilation of some of those findings. In these studies, “we’re seeing less than 5% failure rate with extended (over 5 year) follow-up,” he said.

Dr. Arthur discussed in detail the work being done at William Beaumont Hospital, in Michigan, by Frank A. Vicini, MD. Of 199 interstitial brachytherapy patients, 120 received low dose radiation and 79 got high dose radiation. At a median follow-up of 5 years, there was a

0.5% failure rate at the site of lumpectomy. Elsewhere failure within the breast occurred in 0.6% of patients. Ipsilateral failure (a combined data analysis of both types of failure) was 1.2% and contralateral failure rate was 1%.

The researchers performed a matched-pair analysis, comparing the patients in the study with 700 patients in their database who had received external beam radiation. Patients were matched based on age, tumor size, nodal status, estrogen receptor status, and whether or not they were taking tamoxifen.

They found no statistically significant difference between the two groups with regard to failure endpoints. However, there was a statistically significant increase in contralateral breast cancer failures in patients who had external beam radiotherapy.

Dr. Arthur noted that there are three ongoing Phase III prospective randomized trials examining partial breast irradiation.

He concluded: “The 5-year data with partial breast radiotherapy have produced excellent results in appropriately selected patients. Further studies will be helpful in identifying which patients are suitable for partial breast radiotherapy, the surgical and radiotherapy margin needed, and potential of alternative fractionation schedules.” ■

### Plan to attend the Society of Surgical Oncology's 57th Annual Cancer Symposium



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