SUPPLEMENT TO
MANAGED Care

Advances in Treatment And Management Of Early Breast Cancer

HIGHLIGHTS

• Breast Cancer: An Overview of the Disease

• Advances in Systemic Treatment of Early Breast Cancer in Postmenopausal Women

• Managing Treatment of Early Breast Cancer in Postmenopausal Patients: A Nurse Practitioner’s View

• A Medical Director’s Perspective On Early Breast Cancer

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Advances in Treatment and Management Of Early Breast Cancer

Introduction ........................................................................................................................................3
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Breast Cancer: An Overview of the Disease .................................................................4
JOHN E. PIPPEN JR., MD
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Advances in Systemic Treatment
Of Early Breast Cancer in Postmenopausal Women ........................................10
GENEROSA GRANA, MD
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Robert Wood Johnson Medical School, Cooper Hospital/University Medical Center
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Managing Treatment of Early Breast Cancer
In Postmenopausal Patients: a Nurse Practitioner’s View ..................................16
JUDITH K. MUCH, CRNP, AOCNP, APRN, BC
Oncology Nurse Practitioner, Integrated Oncology Care, Lehigh Valley Hospital
Allentown, Pa.

A Medical Director’s Perspective on Early Breast Cancer .................................22
HARLAN A. LEVINE, MD
Chief Clinical Officer, UnitedHealth Group, Specialized Care Services
Golden Valley, Minn.

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Breast cancer imposes a substantial burden on managed care organizations and their individual members. As the US population ages, this burden is likely to increase. In this supplement, two oncologists (Generosa Grana, MD, and John E. Pippen Jr., MD), an oncology nurse (Judith K. Much, CRNP, AOCNP, APRN, BC), and I (a medical director) share insights about the nature of the disease and strategies to improve outcomes in patients with early-stage breast cancer.

It is incumbent on health plans to adopt a patient-centered approach to early breast cancer, focusing on those issues that are important to the individual. Emphasis should be placed on early diagnosis, sensitivity to the wide range of emotions that patients experience on being diagnosed with breast cancer, appropriate treatment that conforms with the patient’s preferences, and efforts to reduce the risk of recurrence.

Tamoxifen has been the mainstay of adjuvant drug treatment aimed at reducing the risk of recurrence, which is associated with increased morbidity, mortality, and cost. Yet, in light of the emergence of new information about the utility of aromatase inhibitors as adjuvant therapy, such as that provided by the Arimidex, Tamoxifen, Alone or in Combination (ATAC) study (Howell 2005), oncologists may have more options in the future. Early indications are that, in comparison with tamoxifen, aromatase inhibitors increase disease-free survival for postmenopausal women with hormone receptor-positive early-stage breast cancer, which represents the majority of cases. Oncologists and patients should be heartened to know that their options for addressing breast cancer recurrence are expanding.

It should be remembered, however, that drug therapy is just one component among many in a comprehensive approach to breast cancer management and treatment — and, as the article by Much makes clear, that the team of health care providers entrusted with delivering comprehensive care is headed by the patient.

Reference
Breast cancer is a malignant tumor that has developed from cells in the breast and that can spread to other areas of the body, such as the liver, skin, bones, brain, or lungs. Survival, defined as alive and disease-free at greater than 5 years from diagnosis, has improved in the past several decades (Jemal 2005) via better screening, earlier detection, and improved treatment and monitoring (Elmore 2005). Nevertheless, instances of some types of cancer, such as ductal carcinoma in situ (DCIS), have risen, most likely because increased routine screening has led to increased detection of early-stage cancers (Huston 2005).

Among women, breast cancer is the second leading cause of cancer deaths, after lung cancer. Breast cancer is also the most common cancer in women after non-melanoma skin cancer. In the United States in 2005, an estimated 211,240 new cases of breast cancer will be diagnosed in women, and an estimated 40,410 women will die from the disease. Lifetime risk for a woman is 1 in 7 (ACS 2005). The disease is most prevalent in North America, closely followed by other developed countries; as countries develop, risk rises. Most notably, risk rises with age; 80 percent of breast cancers occur in post-menopausal women. Inheritance of a faulty gene is the cause of only 5 percent to 10 percent of breast cancers (BCC 2005).

Men can also develop the disease, and account for 1 percent of all breast cancer diagnoses. In the United States in 2005, an estimated 460 men will die from breast cancer (ACS 2005), and men with breast cancer have a greater chance of developing prostate cancer.

### RISK FACTORS

Each woman has a unique combination of risk factors for developing breast cancer, and it is hard to predict who will develop the disease. Risk factors include sociodemographic, hereditary, and physical conditions. Many women with hereditary potential (ie, strong family history of breast cancer) do not develop the disease, and vice versa. Women who previously have had breast cancer, particularly if they were diagnosed at an early age, are at a greater risk of developing breast and other cancers, specifically ovarian cancer. Studies suggest that early menarche, delayed or absent parity (childbearing), lack of breastfeeding, and delayed menopause contribute to heightened estrogen levels, consequently increasing the risk of breast cancer. These hormonal conditions are common in women in developed countries.

Age is the most significant risk factor, possibly because of lifetime exposure to factors that increase damage to genetic material in the breast cell. Moderate risk factors are shown in Table 1 and slight risk factors are shown in Table 2.

### GENETICS OF BREAST CANCER

Women with a family history of breast cancer represent only 5 to 10 percent of all women with breast cancer. While it is possible to inherit altered genes that increase the risk of cancer, all breast cancer is genetic in the sense that it arises from mutations of genetic material in cell DNA (Blachford 2002). These mutations are caused by conditions internal and external to the body. For example, current and recent users of hormone replacement

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**TABLE 1 Moderate risk factors for developing breast cancer**

- **Increased age.** About 77 percent of women diagnosed with breast cancer each year are over age 50, and almost half are age 65 and older; increased risk with age is possibly from lifetime exposure to hormones.
- **Direct family history.** A first-degree relative (eg, mother or sister) with breast cancer, especially if the relative was diagnosed at a young age.
- **Genetics.** Carriers of mutations in one or both of the breast genes BRCA1 and BRCA2 account for 10 percent of breast cancer diagnoses; mutations in other genes (such as p53) also increase risk.
- **Personal history of benign or cancerous breast disease.** Benign breast disorders, such as atypical hyperplasia and lobular carcinoma in situ, increase the risk of developing breast cancer (Hartmann 2005), as does having had breast cancer previously.
- **Postmenopausal breast density.** High breast density after menopause increases risk.

SOURCE: ADAPTED FROM ACS 2003, 2005

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therapy (HRT) are at increased risk for developing breast cancer, though the risk seems to return to that of the general population within 5 years of stopping HRT (ACS 2005). Table 3 lists known genetic mutations that confer an increased likelihood of developing breast cancer.

**Oncogenes**, or genes that promote cell division, encourage cancer when “turned on” by mutation, leading to rapid cell replication in the host tissue. **Tumor-suppressor genes**, such as genes p53, BRCA1, and BRCA2, slow down cell division; mutations that “turn off” tumor-suppressor genes can be inherited or caused by external factors such as viruses that have tumor suppressor-inactivating genes in their DNA.

Several genes that affect breast and ovarian cancer risk are autosomal recessive, which means a woman will not develop breast cancer if she has inherited a normal version of the gene from at least one parent. Nonetheless, even normal genes can be damaged by environmental causes, i.e., carcinogens, including:

- Tobacco products (eg, cigarettes and cigars)
- Pollutants: chemicals (eg, pesticides that act like estrogens)
- High-dose radiation

**TYPES OF BREAST CANCER**

Breast cancer is classified by a woman’s menopausal status, whether the cancer has spread, the size and location of the tumor, genetics, hormone receptor status of the tumor, and the nature of cell nuclei.

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**TABLE 2** Slight risk factors for developing breast cancer

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Distant family history. Relatives beyond the first-degree (eg, grandmother or cousin) with breast cancer.</td>
</tr>
<tr>
<td>• Other cancer in family history. Relatives with cancer of the ovaries, cervix, uterus, or colon.</td>
</tr>
</tbody>
</table>
| • Hormonal conditions:  
  - Late or absent parity. Bearing a child at >30 years of age, or never.  
  - Lack of breastfeeding of a child. In women with or without children.  
  - Early menarche. Beginning menstruation at <12 years of age.  
  - Late menopause. Ending menstruation at >55 years of age. |
| • Obesity. Especially if developed after menopause; perhaps because fat tissue produces small amounts of estrogen. |
| • Excessive radiation. Especially in women given radiation for post-partum mastitis, or who received prolonged fluoroscopic x-rays for tuberculosis, or who were exposed to a high dose of radiation at <30 years of age. |
| • Ethnicity. Caucasians and those of Ashkenazi Jewish heritage are at increased risk; individuals of minority ethnicity in the United States are more likely to be diagnosed at advanced stages of disease and consequently experience higher mortality rates. |
| • Alcohol consumption of more than 2 drinks per day. Alcohol is thought to increase estrogen and androgen levels in the body. |

ADAPTED FROM ACS 2003, 2005

**TABLE 3** Common genetic mutations that confer increased likelihood of developing breast cancer

<table>
<thead>
<tr>
<th>Gene name</th>
<th>Implications for increased risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1 or BRCA2</td>
<td>5 percent of women have 1 unhealthy copy of BRCA1 (Blachford 2002). Women with an inherited BRCA1 or BRCA2 mutation have up to an 80 percent chance of developing breast cancer during their lifetime. Women with these inherited mutations also have an increased risk for developing ovarian cancer. Trend is slightly higher in some isolated ethnic cultural populations such as Ashkenazi Jews (ACS 2005).</td>
</tr>
<tr>
<td>P53</td>
<td>Li-Fraumeni syndrome.</td>
</tr>
<tr>
<td>PTEN</td>
<td>Cowden’s syndrome.</td>
</tr>
<tr>
<td>ATM (ataxia-telangiectasia mutation)</td>
<td>This gene is responsible for repairing damaged DNA; certain families with a high rate of breast cancer have been found to have mutations of this gene.</td>
</tr>
<tr>
<td>CHEK-2</td>
<td>One variant of this gene results in an approximately twofold increase of breast cancer risk in women and a tenfold increase in men. The variant confers no increased cancer risk in carriers of BRCA1 or BRCA2 mutations.</td>
</tr>
</tbody>
</table>

ADAPTED FROM ACS 2005, BLACHFORD 2002
Two noninvasive breast lesions include ductal carcinoma in situ (DCIS) — in ducts, and lobular carcinoma in situ (LCIS) — in lobules (milk-producing glands). Table 4 describes the characteristics of DCIS and LCIS. Figures 1 and 2 show breast tissue and the common locations of breast cancer.

The most common type of breast cancer is infiltrating (invasive) ductal carcinoma (IDC), which originates in a milk duct. A less common type of invasive cancer originates in a breast lobule. Table 5 lists comparisons of these two types of invasive breast cancer.

Rare types of breast cancer, comprising less than 5 percent of all breast cancers, include medullary carcinoma, Paget’s disease, inflammatory breast cancer, phylloides tumor (rarely malignant), and tubular carcinoma. Table 6 lists tests used to diagnose the presence and type of breast cancer.

### Table 4: Common breast adenocarcinomas (cancers in situ)

<table>
<thead>
<tr>
<th>Name</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ductal carcinoma in situ (DCIS)</td>
<td>• Early form of noninvasive breast cancer.</td>
</tr>
<tr>
<td></td>
<td>• Sometimes called intraductal or noninvasive.</td>
</tr>
<tr>
<td></td>
<td>• Localized inside milk ducts.</td>
</tr>
<tr>
<td></td>
<td>• Cancer cells do not spread elsewhere in or beyond breast.</td>
</tr>
<tr>
<td></td>
<td>• Diagnosed frequently by micro calcifications, usually by mammogram.</td>
</tr>
<tr>
<td></td>
<td>• Has three grades (high, intermediate, low) based on microscopic exam of tissue.</td>
</tr>
<tr>
<td></td>
<td>• Increase in grade value corresponds to likelihood of progression to invasive disease.</td>
</tr>
<tr>
<td>Lobular carcinoma in situ (LCIS) (also called lobular neoplasia)</td>
<td>• Sometimes classified as a precancerous lesion, but more accurately, as a marker for increased risk for subsequent development of invasive cancer.</td>
</tr>
<tr>
<td></td>
<td>• Originates in the lobule (milk-producing gland) and does not penetrate through the wall of the lobule.</td>
</tr>
<tr>
<td></td>
<td>• Women with this condition have a higher risk of developing an invasive breast cancer in the same breast or the other breast.</td>
</tr>
</tbody>
</table>

ADAPTED FROM ACS 2005

Grade 2 (moderately differentiated) cancers have features between grades 1 and 3.
Grade 3 (poorly differentiated) cancers, the highest grade, lack normal features and tend to grow and spread more aggressively.

### Table 5: Comparison of invasive breast cancer types

<table>
<thead>
<tr>
<th>Type</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infiltrating (invasive) ductal carcinoma (IDC)</td>
<td>- Originates in a milk duct. A less common type of invasive cancer originates in a breast lobule.</td>
</tr>
<tr>
<td>Lobular carcinoma (LCIS)</td>
<td>- Originates in the lobule (milk-producing gland) and does not penetrate through the wall of the lobule.</td>
</tr>
</tbody>
</table>

### Table 6: Diagnostic tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammogram</td>
<td>Used to detect breast cancer by examining micro calcifications.</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>Used to detect breast cancer by examining ducts.</td>
</tr>
<tr>
<td>Fine needle aspiration biopsy</td>
<td>Used to diagnose the presence and type of breast cancer.</td>
</tr>
</tbody>
</table>

### Diagnostic Methods and Prognostic Indicators
Factors that affect prognosis are tumor size, location, stage, and molecular characteristics (eg, estrogen receptor, progesterone receptor, HER2/neu), histological characteristics, and patient characteristics (ie, age, menopausal status, and family genetic history).

Grading of an invasive cancer helps achieve a more accurate prognosis. Histologic tumor grade is based on the arrangement of cancer cells in relation to each other, and how many of the cancer cells are in the process of dividing (mitotic count).

Grade 1 (well-differentiated) cancers have relatively normal-looking cells that do not appear to be growing rapidly and are arranged in small tubules.
DCIS (noninvasive) cancer is sometimes given a “nuclear grade” based on how abnormal the cancer cells are, and any presence of necrosis (dead or degenerating cancer cells) also is noted (ACS 2005).

**PREDICTIVE FACTORS**

Molecular characteristics of breast cancer serve as both prognostic and predictive factors.

Estrogen and progesterone sensitivity are indicated by the presence of receptors for these hormones. Tumors are referred to as ER positive (estrogen sensitive) or PR positive (progesterone sensitive), or simply hormone positive. Patients with hormone-positive tumors tend to have a better prognosis and are much more likely to respond to hormone therapy (predictive for response) than women whose tumors lack these receptors.

Approximately one third of breast cancers have too much of a cell-growth-promoting protein called HER2/neu. HER2/neu-positive tumors have too many (more than two) copies of the gene that instructs cells to produce HER2/neu protein expressed on the surface of the cell. HER2/neu-positive tumors tend to grow and spread more aggressively than other breast cancers. HER2/neu-positive tumors respond better to anthracycline chemo-
therapy drugs than HER2/neu-negative tumors, and also can be treated with trastuzumab — an antibody to the HER2 receptor that prevents the protein from stimulating cell growth (Johns Hopkins 1998).

Other predictive tests evaluate the p53 tumor-suppressor gene, epidermal growth factor receptor, microvessel density (the number of small blood vessels that supply oxygen and nutrition to the cancer), genes that stimulate microvessel growth, and ploidy (number of sets of chromosomes in a cell).

Combining prognostic and predictive information of the breast cancer informs treatment choices pertaining to adjuvant chemotherapy. Assessing the HER2/neu, ER/PR status, and proliferation rate helps classify the aggressiveness of the cancer and potential for metastasis.

STAGING

Types of metastasis include regional (cancer has spread into lymph nodes) and systemic (cancer has spread to other parts of the body such as lungs, bones, liver, skin, and soft tissue). Breast cancer often progresses to become systemic early in the course of disease (Thackery 2002). The presence of cancer in lymph nodes, the number of nodes affected, and tumor size are the best indicators of metastasis. Figures 1 and 2 show breast tissue and the common locations of cancer.

By the time it is noticed, a tumor is usually 1 centimeter in size, has been growing for 1 to 5 years, contains a billion cells, and may already have spread. Micrometastases are minute cancer deposits in other organs and are hard to detect. The tests in Table 7 are used to detect metastasis. The extent of metastasis determines the stage of cancer.

Staging is done after node status has been established by surgery and before administering treatment. Table 8 shows the five stages and their characteristics.

Assessment of a patient’s unique clinical situation determines which adjuvant therapy is most likely to decrease the risk of recurrence, and includes consideration of age, general physical condition, and tumor characteristics.

LIVING WITH BREAST CANCER

During treatment for breast cancer, patients experience a range of physical and emotional effects depending on the treatment method. Most patients also experience some degree of “posttreatment syndrome,” struggling with feelings of depression and confusion, a sense of loss, fear of recurrence, and a desire to reengage in their lives, living a healthier lifestyle physically and emotionally (Shockney 2002). The risk of recurrence is reduced by pharmaceutical and surgical treatments. For individuals at a high risk of developing breast cancer, either for the first time or a new primary, the risk/benefit of different preventive strategies is weighed. Preventive strategies include changes in diet, taking a medication such as tamoxifen to prevent cancer development, an exercise program, prophylactic surgery (eg, mastectomy), and chemoprevention.

Breast cancer is a diverse disease among those who
develop it. Fortunately, survival rates have been improved by increased awareness and education about the disease, including increased routine screenings. Our ability to characterize the clinical nature of tumor tissue and to classify the type of disease also has extended disease-free years of life and has reduced mortality (Harvard Women’s Health Watch 2004). Now, more than 90 percent of stage I patients and over 80 percent of stage II patients survive. Those with stage III cancer survive in about 50 percent of cases, and those with stage IV in 20 percent of cases (ACS 2005). Treatment advances are tending toward a preventive model, and improvements in general allow more individualized diagnosis, prognosis, and treatment.

References


BCC (Breast Cancer Care). Available at: «http://www.breastcancercare.org.uk/». Accessed Sept. 6, 2005


SPECIFICALLY, ANTHRACYLINE-BASED POLYCHEMOTHERAPY WITH FAC OR FEC REGIMENS REDUCED THE ANNUAL RISK OF DEATH BY APPROXIMATELY 20 PERCENT IN WOMEN 50 TO 69 YEARS OF AGE. FOR PATIENTS WITH HR-POSITIVE TUMORS, 5 YEARS OF ADJUVANT TAMOXIFEN REDUCED THE ANNUAL BREAST CANCER DEATH RATE BY 31 PERCENT IN ALL AGE GROUPS. THE REDUCTIONS WERE ADDITIVE, SO THAT IN HR-POSITIVE WOMEN 50 TO 69 YEARS OF AGE WHO HAD BEEN ON AN ANTHRACYLINE-BASED CHEMOTHERAPY REGIMEN FOLLOWED BY 5 YEARS OF TAMOXIFEN, THE TOTAL RISK REDUCTION WAS 45 PERCENT. TRASTUZUMAB, TOO, HAS BEEN SHOWN TO REDUCE RECURRENCE RISK BY 52 PERCENT AFTER 3 YEARS IN HER2/NEU-POSITIVE CANCERS WHEN ADDED TO CHEMOTHERAPY. THIS DRAMATIC REDUCTION LED TO A MUCH IMPROVED SURVIVAL RATE AT 4 YEARS AND A SIGNIFICANT OVERALL SURVIVAL BENEFIT (ASCO 2005).

ALL THE MAJOR CLASSES OF ADJUVANT THERAPY—CHEMOTHERAPY, BIOLOGIC TREATMENT, AND HORMONAL THERAPY—HAVE RESULTED IN SIGNIFICANT RISK REDUCTIONS FOR RECURRENCE AND MORTALITY WHEN USED IN APPROPRIATE PATIENTS. THE CHALLENGE FOR THE CLINICIAN IS TO DETERMINE WHICH PATIENTS SHOULD RECEIVE THESE AGENTS AS INITIAL ADJUVANT THERAPY AND WHETHER THESE AGENTS SHOULD BE USED ALONE OR IN COMBINATION—CONCURRENTLY OR SEQUENTIALLY.

PROGNOSIS OF BREAST CANCER


A USEFUL RESOURCE FOR ADJUVANT THERAPY DECISION MAKING IS A WEB SITE HOUSING AN ALGORITHM TO PREDICT RECURRENCE RISK: «WWW.ADJUVANTONLINE.COM». THIS ALSO HELPS CLINICIANS TO ASSESS A PATIENT’S PROGNOSIS AND TREAT-
ment effectiveness in the context of available clinical trial data.

**Other decision-making tools**

Gene expression-profiling tools are available commercially, which may help the oncologist formulate a prognosis and support a treatment plan. Although these tests are not yet — and may never be — a sole indicator of which categories of drugs to use, they are valuable when a physician is debating between two treatment courses. Tissue microarray profiling allows multigene screening of the specific tumor to predict risk of metastasis and recurrence using a “recurrence score” (Paik 2004). This test can be performed on a small piece of paraffin-embedded tissue obtained from the initial diagnostic procedure. Costing approximately $3,500, this test has demonstrated value in a select patient group — lymph-node negative, stage I or II, and hormone receptor-positive. Studies in broader subgroups of patients are ongoing. In a case, for example, in which a woman has a node-negative, estrogen receptor-positive tumor under 4 centimeters in size, genotyping can clarify prognosis and help with the decision of whether to use chemotherapy, hormone therapy, or both. Both the Oncotype DX 21-gene array profile (Genomic Health) and the “Amsterdam” technique, developed by the Netherlands Cancer Institute, await broader testing (Bast 2004).

**GUIDELINES FOR TREATMENT**

Without guidelines and treatment algorithms, decision-making for adjuvant therapy would be difficult, and explaining options to a patient would be nearly impossible. Up-to-date guidelines are available from the National Comprehensive Cancer Network; these guidelines have reached a broad audience and have been adopted by many clinicians (Bennett 2003). Future studies will reveal whether the guidelines have resulted in improvements in the quality of medical care.

The goal of systemic therapy for early breast cancer is to eliminate microscopic disease known as micrometastases. Currently approved systemic therapy options include:

- Chemotherapy to kill rapidly dividing cancer cells
- Hormonal therapy using a third-generation nonsteroidal aromatase inhibitor such as anastrozole or letrozole or the steroidal aromatase inhibitor exemestane to block estrogen production, or using tamoxifen to block the stimulatory effects of estrogen via the estrogen receptor

**Chemotherapy**

The goal of chemotherapy is to prevent recurrences and relapse with the fewest number of side effects, the greatest degree of cost-effectiveness, and the highest quality of life. Typically, 4 to 6 cycles of chemotherapy are given at 2- to 3-week intervals. Chemotherapy consists primarily of cytotoxins that kill the rapidly dividing cells; polychemotherapy has been demonstrated to substantially improve long-term relapse-free and overall survival, respectively, in premenopausal and postmenopausal women, up to age 70, who have node-positive and node-negative disease (EBCTCG 2005). Chemotherapeutic agents are administered along with various supportive therapies such as antiemetics or growth factors.

In the EBCTCG’s recent metaanalysis (2005), a reduced risk of recurrence and death was seen with the use of CMF (cyclophosphamide, methotrexate, fluorouracil) versus nil; use of an anthracycline-containing regimen increased the level of benefit. The taxanes (docetaxel and paclitaxel) further add to the survival benefit. Generally, in women age 50 to 59, anthracycline-based chemotherapy reduced mortality by 20 percent. Unfortunately, there were not enough women over 70 years old included to analyze the optimal chemotherapy regimen in this age group.

Although the best combinations of adjuvant agents are becoming clearer, thanks to large clinical studies and metaanalyses, a breast cancer physician still needs to decide in whom to use chemotherapy and which specific agents to select for a given patient.

**Hormonal therapy**

The rationale for hormonal therapy is to deprive the breast tumor of estrogen, which is implicated in tumor progression. In premenopausal women, drugs such as luteinizing hormone-releasing hormone (LHRH) agonists or surgical removal of ovaries switch off the production of ovarian estrogens. Aromatase inhibitors, which block peripheral production of estrogen, are indicated only for postmenopausal women because of the mechanism of action (Table 1, page 12). Tamoxifen, which blocks binding of estrogen to the estrogen receptor, is effective in premenopausal and postmenopausal women.

**HORMONAL THERAPY: RECURRENCE AND BREAST CANCER MORTALITY OUTCOMES**

The use of chemohormonal therapy has cut the annual death rate from estrogen-receptor positive breast cancer in half (EBCTCG 2005), even though many of these regimens included chemotherapy and hormonal regimens that now are considered less than optimal. Nevertheless, one third of node-positive patients died of breast cancer during the first, second, and third decade after diagnosis (EBCTCG 2005). Research continues to determine the best treatment sequence as well as the optimal hormonal agents to reduce this number further.

**Tamoxifen**

Tamoxifen, a selective estrogen receptor modulator (SERM), has been used as an adjuvant hormonal treat-
Aromatase inhibitors

Principally on the basis of large randomized, double-blind trials, the American Society of Clinical Oncology (ASCO) recently recommended that 5 years of tamoxifen should no longer be the standard treatment for patients with early breast cancer, but rather “optimal adjuvant hormonal therapy for a postmenopausal woman with receptor-positive breast cancer should include an aromatase inhibitor either as initial therapy or after treatment with tamoxifen” (Winer 2005). Neither the optimal timing nor duration of aromatase inhibitor therapy has been established, but new data are shedding light on this.

Eventually, clinicians will have access to data regarding more than 40,000 early breast cancer patients enrolled in clinical trials of aromatase inhibitors. To date, however, data have been published in peer-reviewed journals investigating various strategies for employing aromatase inhibitors as adjuvant therapy; preliminary results from some of the other trials have been presented at conferences.

The Arimidex, Tamoxifen, Alone or in Combination (ATAC) study of anastrozole as early adjuvant therapy is the largest clinical trial of aromatase inhibitors thus far, and the one in which patients have been followed the longest (Howell 2005). (See Table 3, page 14 for important safety information and indications for anastrozole.) After a median follow-up of 68 months, improved disease-free survival was seen in anastrozole-treated patients (Table 4, page 14).

The Intergroup Exemestane Study 031 compared exemestane versus tamoxifen in postmenopausal women with early breast cancer. The patients who had remained disease-free after 2 to 3 years of adjuvant tamoxifen therapy were randomized to either switch to exemestane or remain on tamoxifen for 2 to 3 years to complete a total of 5 years of treatment. After a median duration of follow up of 34.5 months, disease-free survival was improved by 31 percent in the exemestane-treated patients compared to patients who remained on tamoxifen. Overall survival was not significantly different in the two groups.

The only trial of aromatase inhibitors as extended adjuvant therapy (ie, after the completion of 5 years of tamoxifen therapy) that has been published thus far is MA.17, for which updated findings recently were provided (Goss 2005). After the completion of tamoxifen therapy, disease-free patients were randomized to letrozole or placebo, and after a 30-month median follow-up, recurrence risk was 42 percent less in letrozole-treated patients compared with patients who received placebo ($P<.001$). Although there was no overall difference in all-cause mortality between the letrozole and placebo arms, among node-positive patients the risk of all-cause mortality was reduced by 39 percent in the letrozole group ($P=.04$).

Biologic therapy

While 70 percent of malignant tumors are HR positive, only 25 to 30 percent are HER2/neu-positive, meaning that the patient has more than two copies of the HER2 gene and cells produce too much of the HER2/neu protein, which fuels cell replication and breast cancer growth. If the tumor is HER2/neu-positive against the HER2 receptor, it may be susceptible to biologic therapy.
that keeps HER2/neu from transmitting growth signals to breast cancer cells.

There are encouraging early data from three adjuvant trials among high-risk lymph node-negative patients and lymph node-positive patients, including a combined analysis of the North Central Cancer Treatment Group (NCCTG) N9831 and NSABP B-31.

**CONCLUSION**

Advances in hormonal therapy, chemotherapy, and ongoing research in biologic therapy have allowed clinicians to evaluate a multipronged approach to lowering risk of recurrence, greatly increasing disease-free survival rates. Large clinical trials such as ATAC are helping to establish the role of aromatase inhibitors in hormonal...
therapy. Ongoing research likely will lead to better tools to assess prognosis and predict treatment outcomes, as advances in drug discovery continue to assist in the fight against breast cancer.

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Breast cancer is a heterogeneous disease, necessitating individualized care. Most patients with early (operable) breast cancer, regardless of age or menopausal status, are presented with a menu of options for treatment, including surgery, radiation therapy, chemotherapy, and hormonal agents. The range of choices is overwhelming for most patients, and even with clear guidance, they continue to seek information from the popular press, the Internet, family, and friends. Unless they happen to pick accurate sources, they can become confused about their prognosis and appropriate care. Care of a breast cancer patient can be accomplished optimally through coordinated case management, counseling, and emotional and informational support. The health care team provides its most valuable service by assisting patients in facing these difficult decisions, learning to live with a cancer diagnosis, and by providing comfort and support throughout diagnosis, treatment, and surveillance.

THE ONCOLOGY NURSE’S ROLE

The cancer care team comprises the primary care physician, medical oncologist, radiation oncologist, surgeon or surgical oncologist, pathologist, social worker, case manager, and the oncology nurse, with the latter sometimes spending the most time with the patient. The oncology nurse thus is ideally positioned to provide a consistent message over time by individualizing and coordinating care services. Yet, at the heart of nursing is the understanding that the patient and her family are the head of this team.

The nurse’s duties depend on educational level and scope of practice. These duties can range from handling crises to routine care to telephone triage expediting symptom management. Maintaining the patient’s emotional well-being involves coaching her through anxiety and fear while making long-term plans to reduce her overall health risk and minimize the disease’s psychosocial effects.

Nurses often can improve outcomes by informing decisions and reintegrating patients into the community during surveillance. Although the majority of relapses occur within the first 5 posttreatment years, elevated recurrence risk persists for 20 years (Rosen 1993). Unfortunately, the recurrence risks and importance of proper medical surveillance must be made clear to the patient when she is trying to put the experience behind her. Patients should be connected with educational resources regarding recurrence risk and preventive measures, and they may need to be reminded to continue medication throughout years of surveillance and monitoring. Often patients believe “a pill” is not as strong or important as other medications used for cancer.

CONNECTING THE PATIENT WITH RESOURCES

An important role for the nurse is connecting patients with resources. For example, if the patient cannot pay for a medication, a nonprofit organization such as the American Cancer Society may be able to help. In addition, each pharmaceutical company has its own patient assistance program (Table 1).

The office business staff or social worker usually manages reimbursement, but the nurse often must cope with clinical conflicts that arise from a patient’s inability to obtain a medication because it is not on formulary. A health care plan may cover a less-effective antinausea medication but not a newer, more effective one. Similarly, the plan may pay for an Infusoport but not for maintenance syringes or flushing units, meaning extra inconvenience for patients who must return to the practitioner’s office to flush the unit.

Payors sometimes follow Medicaid or Medicare formularies without researching the effect on patient care. Patients’ needs are highly individualized, while formularies are designed to standardize treatment. Oncology nurses often provide documentation to managed care formularies to provide “medical necessity” for off-formulary dispensing.

Emotional and spiritual support for patients who are living with cancer can be achieved through family, support groups, individual counseling, and religious organizations. In the book *The Anatomy of Hope*, Groopman illuminates ways to tell the truth without incurring de-
spair and to provide hope without misleading patients, arguing that hope has a biological healing effect.

With shorter postsurgery hospital stays, an increased amount of early care after surgery falls on the patient’s family. Often, the caregiver needs emotional support. Books by caregivers and support groups have helped others cope when they find themselves to be caregivers overnight. Patient education and counseling are aided by organizations, publications, and Web sites (Table 1).

During this time of decision-making, much care and sensitivity must be given to the patient. Sending the patient to specific informational Web sites is preferable to their surfing the Internet and finding disconcerting, contradictory, or confusing information that may not be pertinent to the patient’s clinical situation. It is important to tailor the information to the needs of the patient, depending on the patient’s educational level, culture, personality type, and level of sophistication. Most patients will need additional information. When patients and their caregivers receive feedback on their condition while in a state of high anxiety, they forget most of what is said.

**CLINICAL MANAGEMENT**

**Diagnosis.** Diagnosis of breast cancer is made by fine needle aspiration, core needle biopsy, stereotactic biopsy, needle, wire localization, or incisional or excisional biopsy. Management of breast cancer depends on the diagnosis: tumor size, lymph node status, predictive/prognostic markers (most importantly, estrogen receptor [ER] and progesterone receptor [PR] status and HER2/neu), menopausal status, and performance status.

During this most important time for the patient, the nurse has a key role in educating the patient and family regarding the techniques used for diagnosis: eg, what to expect, how to prepare, and how to manage discomfort or symptoms following diagnostic procedure. Following the diagnosis, the nurse guides the patient through interpretation of the operative and pathologic findings, and helps to coordinate the next step in the process. Certainly at this time, as at other key points in the cancer care trajectory, clear, concise explanations are necessary, and the nurse’s role is pivotal in that respect.

**Treatment.** The role of nurses in managing women who are diagnosed with breast cancer is well demonstrated in the treatment of the elderly. Controversy persists in the medical community over what constitutes appropriate care for the older postmenopausal woman with breast cancer. While the mortality rate for breast cancer has declined for women under age 70, it has been steady in women ages 70 to 79, and it has increased in women over age 80. This is likely to be related to undertreatment (Bouchardy 2003). Older women are perceived as having less aggressive breast cancer than younger women. Any comorbidities could make standard treatment challenging.

**Oncology case management.** In treating older women with breast cancer, the involvement of nurse case managers has resulted in improved management (Goodwin 2003). Nurse case managers offer highly individualized interaction with the patient, sometimes extending to home or hospital visits, accompanying her to the physician and to other appointments, and speaking with her family. Often, the caregiver needs emotional support. Any comorbidities could make standard treatment challenging.

### TABLE 1 Patient resources

**Web sites**
- American Cancer Society [www.cancer.org](http://www.cancer.org)
- Dana Farber/Brigham and Women’s Cancer Center [www.brighamandwomens.org/bwhcancer/cancer](http://www.brighamandwomens.org/bwhcancer/cancer)
- Look Good...Feel Better [www.lookgoodfeelbetter.org](http://www.lookgoodfeelbetter.org)
- National Cancer Institute [www.nci.nih.gov](http://www.nci.nih.gov)
- National Coalition for Cancer Survivorship [www.cansearch.org](http://www.cansearch.org)
- Susan G. Komen Breast Cancer Foundation [www.komen.org](http://www.komen.org)
- Y-ME National Breast Cancer Organization [www.y-me.org](http://www.y-me.org)

**Supportive/educational programs and products**
- I Can Cope — educational program offered by American Cancer Society, with classes taught by health care professionals and other knowledgeable people about issues facing people with cancer (1-800-ACS-2345)
- Reach to Recovery — American Cancer Society program enlisting breast cancer survivors who serve as trained volunteers to support and comfort patients before, during, and after breast cancer treatment, by phone or face to face (1-800-ACS-2345)

**Products**
- Look Good, Feel Better — a free, nonmedical, brand-neutral, national public service program to help women offset appearance-related changes from cancer treatment (1-800-395-LOOK)
- tlc (Tender Loving Care) — American Cancer Society Web site offering products for women diagnosed with or recovering from breast cancer [www.tlccatalog.org](http://www.tlccatalog.org)

**Prescription drug assistance programs**
- PPA Rx – Partnership for Prescription Assistance — free/discount drug programs available in many states (1-800-ACS-2345)
on the telephone, all with the intention of decreasing service fragmentation.

Patients who benefit most from a nurse case manager’s assistance are those facing multiple barriers to optimal care, such as advanced age, chronic debilitating conditions, cognitive impairment, low income, poor social support (unmarried, living alone, or living with a frail spouse), and complex therapy involving multiple providers. The nurse case manager does not recommend one treatment over another but ensures that the patient is aware of all her options, that other members of the cancer care team recognize special circumstances affecting their patient, and that the treatment chosen by the patient is provided.

**Local regional therapy**

If the tumor is small, the patient may be offered breast-conserving therapy (BCT) (lumpectomy plus radiation therapy). This is followed by hormonal manipulation if the tumor is ER positive. The 20-year follow-up of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 randomized trial continues to show equivalency of breast-conserving therapy and modified radical mastectomy (Fisher 2002). Breast-conserving therapy, if feasible, is therefore the National Cancer Institute’s currently recommended standard of care.

More conservative surgical evaluation of axillary lymph nodes via sentinel lymph node biopsy (SLNB) has led to less-intensive postoperative care. Many surgeons have adopted SLNB as the standard of care, based on preliminary interim analyses from studies showing that short-term survival and recurrence rates are similar to those of traditional axillary lymph node dissection (ALND). Long-term survival data are not yet available.

If the tumor is large, a woman may elect to have either mastectomy or neoadjuvant therapy, in which the chemotherapy or hormonal therapy is given prior to surgery to shrink the tumor to facilitate breast conservation. A lymph node dissection (either sentinel or complete) is conducted unless the woman is frail and elderly and the prognostic information gained by the lymph node surgery will not influence the treatment plan. Tumor size and lymph node status dictate the need for radiation, even if the woman proceeds to mastectomy.

Making a decision about surgery (lumpectomy plus radiation vs. mastectomy), with or without breast reconstruction, raises many questions and necessitates coordination between the various practitioners, including the breast surgeon, plastic surgeon, and often the medical oncologist. Patients with a strong family history of breast or ovarian cancer may need genetic counseling prior to surgery to determine the need for bilateral mastectomy and to decrease the high risk of contralateral cancers.

The clinical sequelae of breast cancer surgery can include changes in body image, sexual complications, pain and numbness, shoulder dysfunction, and lymphedema. Clinical management of these sequelae includes counseling, arm exercises, elevation, and massage.

**Radiation therapy**

New techniques in radiation therapy are aimed at shortening treatment, thus minimizing toxicity (Keisch 2005). Advances in whole-breast irradiation include hypofractionation and intensity-modulated radiation therapy (IMRT). Hypofractionated doses have been used once weekly in elderly women, predominantly to reduce local recurrence rates (Maher 1995, Ortholan 2005).

Another advance in radiation therapy is accelerated partial breast irradiation (APBI), which uses either conventional external beam technique or brachytherapy to concentrate the radiation on the local tumor bed where most local recurrences occur. Early results are promising, but data are short-term and confirmatory clinical trials are continuing. Three-dimensional conformal radiation therapy (3DCRT) is a less invasive form of APBI that focuses on a limited portion of the breast, causing less damage to surrounding tissue.

Radiation therapy can cause lymphedema, skin changes, and sensory changes. Management of radiation damage includes acute and long-term effects. Nurses help by advising on symptom-specific measures. Radiation treatment for breast cancer does not cause nausea or taste changes. If skin irritation develops as a reaction to radiation, advice can be given to avert further trauma.

**Systemic therapy**

Following surgery, many patients will be offered chemotherapy, hormone therapy, or both to reduce the risk of recurrence. The type of adjuvant chemotherapy depends on life expectancy, comorbid conditions, molecular characteristics of the tumor (ER, PR, HER2/neu status), and the risk/benefit ratio of giving the treatment.

Tamoxifen’s standing as the preeminent hormone therapy is being challenged (in postmenopausal, ER-positive patients) by the newer, third-generation aromatase inhibitors (AIs) — anastrozole, exemestane, and letrozole.

**Chemotherapy**

In the United States, adjuvant chemotherapy is standard care for node-positive breast cancer. Many combinations of agents are used for chemotherapy, and potential side effects from each combination vary. Also, each drug affects patients differently, and the same pa-
patient can undergo chemotherapy with variable adverse effects after each cycle.

Some side effects are universal for cancer chemotherapy. The most common problem is fatigue, which can lead to dizziness and falls. It is important to evaluate the etiology of fatigue, eg, if the fatigue is a result of anemia, then intervention is possible. Neutropenia is the most serious adverse effect of cytotoxic chemotherapy because it increases the patient’s risk of fever and life-threatening infections. Prior to the onset of chemotherapy-induced neutropenia, prophylactic administration of hematopoietic growth factors should be considered for elderly patients or when high-risk regimens (eg, TAC) are employed.

Advice on sleep, diet, and exercise can help prevent dizziness and falls in the very compromised elderly patient. Although practitioners once advised patients to rest whenever fatigued from chemotherapy, we now know that exercise helps decrease fatigue and other side effects while increasing the patient’s psychological well-being (Mock 2001).

Patients with cancer often have anemia, as a consequence of the cancer or chemotherapy, or both (Groopman 1999). Anemia may cause extreme weakness, dyspnea on exertion, pale skin, headache, loss of concentration, and difficulty sleeping. Anemia often can be managed by weekly subcutaneous injections of erythropoietin.

**Alopecia.** Hair loss (alopecia) is an effect of chemotherapy’s attack on rapidly replicating cells, such as those in hair follicles or bone marrow. This effect, too, is highly variable: One patient can keep her hair while another can lose it all after the first dose of chemotherapy. This generally happens when a patient receives anthracycline-based chemotherapy; hair loss usually occurs about 14 days after the treatment and can start slowly and continue to total baldness. Although alopecia is not serious clinically, it is an emotionally devastating side effect of chemotherapy. Careful counseling regarding the timing of hair loss can help a patient prepare to buy a wig that is similar to her natural hair before the hair comes out.

**Other chemotherapy side effects.** Nausea and vomiting are among chemotherapy’s most disturbing side effects. Chemotherapy regimens are classified by their emetic potential; based on that classification and taking into account patient risk factors for nausea/vomiting, an anti-nausea regimen can be tailored. Patients and families need to be informed as to which antinausea drugs can be used on an as-needed basis and which must be given around the clock. Bowel changes generally can be managed with over-the-counter preparations, but the clinician should instruct the patient on their use. Finally, studies have shown that cognitive dysfunction associated with chemotherapy, popularly known as “chemo brain,” does exist (Tannock 2004). In controlled studies of patients with breast cancer, rates of cognitive dysfunction ranged from 16 to 50 percent.

**Hormonal therapies**

Hormonal therapies, which are aimed at reducing risk of recurrence of breast cancer in the hope of reducing morbidity and mortality, have different adverse effect profiles. The adverse effects associated with hormone therapies should be managed by weighing individual risk factors. Oncology nurses should be equipped to discuss with the patient the risks and benefits of each therapy when it is being considered and after treatment initiation to improve treatment adherence and to minimize the consequences of potential adverse effects.

Unlike the antiestrogen tamoxifen, aromatase inhibitors have no partial agonistic effects on the estrogen receptor and thus are less likely to be associated with estrogenic side effects but more likely to be associated with side effects against which estrogen is thought to be TABLE 2  Adverse events (%) in Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial

<table>
<thead>
<tr>
<th></th>
<th>Anastrozole (n=3092)</th>
<th>Tamoxifen (n=3094)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flashes</td>
<td>36</td>
<td>41</td>
</tr>
<tr>
<td>Joint symptoms, including joint disorder, arthritis, arthrosis, and arthralgia</td>
<td>36</td>
<td>29</td>
</tr>
<tr>
<td>Fatigue/asthenia</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>Mood disturbances</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Fractures, all</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Spine, hip, or wrist</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Wrist/Colles</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Hip</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Spine</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Vaginal bleeding</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Ischemic cardiovascular disease</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Vaginal discharge</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>Ischemic cerebrovascular disease</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Venous thromboembolic events</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>0.2</td>
<td>0.6</td>
</tr>
</tbody>
</table>

SOURCE: ARIMIDEX 2005
protective. Thus, during 68 months of follow-up in a trial comparing tamoxifen and anastrozole, adverse events (Table 2, page 19) that were more likely to be experienced by tamoxifen-treated patients were endometrial cancer, ischemic cerebrovascular disease, venous thrombotic events, deep vein thrombosis, hot flashes, vaginal bleeding, and vaginal discharge, while adverse events more likely to be experienced by anastrozole-treated patients included fractures of the hip, wrist, and spine, and joint symptoms such as arthritis, arthrosis, and arthralgia (Arimedex 2005).

All postmenopausal women should have a bone mineral density (BMD) scan performed with dual-energy x-ray absorptiometry (DEXA) to determine baseline BMD, as well as follow-up DEXA scans periodically to monitor bone loss. Women must be advised to immediately report any vaginal bleeding for prompt investigation by the primary practitioner or gynecologist. Routine transvaginal ultrasounds are not necessary to measure endometrial thickness because, unlike postmenopausal bleeding, it is not a predictor of endometrial cancer and frequently leads to unnecessary biopsies.

Reports about patients’ compliance with AI treatment in community settings have not yet been published, but a few studies about adherence to adjuvant tamoxifen therapy are available. Although compliance with tamoxifen therapy in such settings has been found to be better than compliance with other drug treatments for other chronic conditions (Partridge 2003), compliance with tamoxifen therapy is not optimal. In a community-based study of women newly diagnosed with stage I or stage II breast cancer, 15 percent discontinued tamoxifen after about 2 years of follow-up (Demissie 2001). In this study, women who reported side effects were more likely to discontinue tamoxifen, but side effects were more likely to be reported by women whose emotional health was worse at baseline and by patients younger than age 75. In addition, this study highlighted the importance of effective communication, as patients’ confidence in their abilities to communicate with their physicians was associated with increased compliance.

To probe more deeply into the reasons for tamoxifen discontinuance, patients’ beliefs about the risks and benefits of tamoxifen therapy were studied (Fink 2004). This study enrolled women with newly diagnosed ER-positive breast cancer. During 2 years of follow-up, the prevalence of discontinuance was 21 percent, with the majority of those who stopped taking tamoxifen doing so during the first year. A patient’s age, the complexity of the medication regimen, and side effects were not associated with discontinuation of tamoxifen therapy. Rather, the predictors of tamoxifen discontinuance were having four or more positive lymph nodes (relative risk, 2.5 compared with no positive nodes), and holding neutral or negative beliefs about the risks and benefits of tamoxifen therapy (relative risk, 3.0 compared with positive beliefs).

Taken together, these findings suggest an important role for the nurse oncologist in enhancing rates of compliance with hormone therapy (by being attentive to the patient’s emotional state), in educating patients about the importance of adjuvant therapy and its role in reducing recurrence risk, and in facilitating effective communication between the patient and other members of the cancer care team.

Patients should be instructed to call their practitioner if they decide to stop hormonal medication. Further, they need to let their practitioner know if they are to be hospitalized, particularly when on tamoxifen. Because of increased risk of thromboembolic events, tamoxifen should be stopped if a person is bedridden.

CONCLUSION

The oncology nurse is a pivotal member of the breast cancer care team. Acting as an educator, counselor, mediator, and advocate, the oncology nurse is well positioned to help a patient cope with the wide-ranging implications of a breast cancer diagnosis, the vagaries of treatment, and the vigilance and long-term interventions required thereafter to reduce the risk of recurrence. By integrating care, linking patients to the many cancer resources, and engaging families in cancer care teams, nurses can improve outcomes for breast cancer. The experience for the patient and the managed care organization can be optimized by keeping care as seamless as possible and sensitively informing the patient of the rationale, risks, and benefits of treatment and monitoring.

References
Arimedex (anastrozole) [prescribing information]. Wilmington, Del.: AstraZeneca Pharmaceuticals LP. September 2005.


The mountains of statistics with which medical directors necessarily concern themselves on a daily basis tend to conceal the fact that all the abstract data points ultimately represent real people with very real hopes and fears. Fear, more than hope, is foremost in the mind of a woman with newly diagnosed breast cancer. With emotional reactions often dominating logical thought, such news tends to be overwhelming. In this article, I will address the real-life issues that breast cancer patients face every day, whether they are living with this condition or with a history of the condition, and therefore also living with the sobering possibility of recurrence.

It is my hope that, armed with knowledge of recent advances in the treatment of breast cancer (Editor’s note: see “Advances in Systemic Treatment of Early Breast Cancer in Postmenopausal Women,” pp. 10–15), medical directors can promote programs that will be able to raise the hopes and allay the fears of their members with breast cancer. Moreover, because medical directors view breast cancer from a perspective that encompasses the entire spectrum of the disease, ranging from strategies that are aimed at prevention and early detection to the long-term surveillance of patients who have been treated previously, they are well positioned to advocate a wide range of interventions that could attenuate breast cancer’s substantial burden within their managed population (Table 1).

ECONOMIC BURDEN OF BREAST CANCER

Direct and indirect medical costs for breast cancer vary widely, depending on the disease stage. It has been estimated that in the United States breast cancer accounts for about 15 to 20 percent of all cancer costs (Radice 2003), which in 2001 amounted to $157 billion (direct costs, $56 billion; indirect morbidity costs, $16 billion; indirect mortality costs, $85 billion).

In an employed population of women age 50 to 64 years, average annual direct and indirect costs for breast cancer patients were higher than those for patients with osteoporosis or cardiovascular disease (Table 2, page 24). Compared with matched control subjects without cancer, employed breast cancer survivors report losing 4 times as many days from work (21.0 vs. 5.7) in the previous 12-month period (Yabroff 2004). The authors note that this measure underestimates the effects of breast cancer on productivity because it omits working-age people without jobs who were unable to work because of poor health.

CHANGING DEMOGRAPHICS

Today, about 3.5 percent of the US population — 9.8 million people — are cancer survivors, compared with 1.5 percent (3 million people) of the US population in 1971 (MMWR 2004). The 2.2 million Americans who ever have received a diagnosis of breast cancer account for the largest proportion of this group: 22 percent. Numerous factors contribute to the increased number of cancer survivors: increased screening with mammography leading to earlier diagnosis; improved treatment; prevention of cancer recurrence; prevention of advanced disease, reduced mortality from other causes (eg, myocardial infarction); and an increase in the number of older persons, who account for the majority of new cancer cases in general, and breast cancer in particular.

Regardless of the kind of health plan with which a medical director is associated, demographic changes dictate that breast cancer will become a matter of increasing concern. Currently, about 178 million Americans are enrolled in MCOs — approximately half of whom are females facing the well-publicized 1-in-8 lifetime risk of breast cancer. Those who are not yet old enough for, or do not have known inherited risk warranting yearly mammography, are candidates for educational programs that will heighten their awareness of breast cancer.

Because of the aging of the population in the United States, the number of postmenopausal women will continue to increase, along with the subset of postmenopausal women eligible for Medicare because they have attained age 65 (Figure, page 24). The population depicted in the figure (women age ≥50) represents the age group in which about 78 percent of new cases of invasive breast cancer and 86 percent of breast cancer deaths occur (ACS 2003).

In any health plan, it is the responsibility of the medical director to make sure that a system is in place to support breast cancer patients in obtaining the information to help them understand their treatment options. A system established in a commercial plan may differ in some respects from one set up for a Medicare population, but
all will be aimed at the same goal: helping a woman diagnosed with breast cancer maximize the likelihood of a positive outcome and minimize the chance of recurrence.

HELPING BREAST CANCER PATIENTS
At the time of diagnosis, it is essential for the clinician to explain the differences among the stages of breast cancer and the levels of aggressiveness of the tumor. The patient with stage I breast cancer may not readily grasp the fact that her cancer has been diagnosed at an early stage when it is still confined to the breast (and perhaps local lymph nodes) and surgical treatment is likely to be highly effective in removing detectable disease. Patients may find comfort in learning that today the 5-year survival rates for localized and regional breast cancer are 98 percent (compared with 80 percent in the 1950s) and 80 percent, respectively (ACS 2005). Telling patients about the sophisticated techniques used to determine staging and aggressiveness, along with the reasons for determining the HER2/neu status and the estrogen/progesterone receptor status of their tumors, also may be beneficial in helping them understand the nature of their disease and its prognosis. It is important to explain that detecting markers of aggressiveness (such as HER2/neu status) can help in making the decision for a more aggressive treatment plan that can increase the chances of long-term survival.

In this context of hopefulness, clinicians then can assist the patient in drawing a mental map depicting the path that is most likely to lead to a positive outcome. This map would address the multidisciplinary services pro-

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**TABLE 1** Burden of female breast cancer in the United States

<table>
<thead>
<tr>
<th>Measure</th>
<th>Units</th>
<th>Breast cancer rank order</th>
<th>Rank of other cancers in proximity to breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cancer survivors</strong></td>
<td>2.2 million (22% of all living Americans ever diagnosed with breast cancer)</td>
<td>1</td>
<td>2. Prostate (17%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3. Colorectal (11%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4. Gynecological (10%)</td>
</tr>
<tr>
<td><strong>New cases of invasive breast cancer, 2005</strong></td>
<td>211,000*</td>
<td>1 (women)</td>
<td><strong>WOMEN</strong></td>
</tr>
<tr>
<td></td>
<td>(32% of the 663,000 new cancer cases among women; 15% of the 1.4 million new cases among both sexes)</td>
<td></td>
<td>2. Prostate (17%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 (both sexes)</td>
<td>3. Colorectal (11%)</td>
</tr>
<tr>
<td><strong>Deaths, 2005</strong></td>
<td>40,000</td>
<td>2 (women)</td>
<td><strong>WOMEN</strong></td>
</tr>
<tr>
<td></td>
<td>(15% of the 275,000 cancer deaths among women; 7% of the 570,000 cancer deaths among both sexes)</td>
<td></td>
<td>1. Lung and bronchus (26%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 (both sexes)</td>
<td>2. Colorectal (10%)</td>
</tr>
<tr>
<td><strong>Person-years of life lost from cancer, 1997</strong></td>
<td>809,000</td>
<td>2</td>
<td>1. Lung and bronchus (2.2 million)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3. Colorectal (758,000)</td>
</tr>
<tr>
<td><strong>Average years of life lost per person from cancer, 1997</strong></td>
<td>19.3</td>
<td>6</td>
<td>1. Childhood (69.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. Testis (34.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3. Hodgkin’s lymphoma (26.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4. Cervix uteri (25.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5. Brain and other nervous system (21.9)</td>
</tr>
</tbody>
</table>

*The ACS also predicts 50,000 new cases of ductal carcinoma in situ (DCIS) in 2005, the majority of which, without treatment, will progress to invasive cancer.

vided by a comprehensive health care team, including surgical options, radiation therapy, chemotherapy, hormonal therapy, immunotherapy, long-term surveillance following the initial therapy, and support services. Because some patients may associate cancer treatment of any kind with unproven and potentially dangerous experimentation, an explanation that the health plan endorses the use of evidence-based guidelines, such as those that are promulgated by the National Comprehensive Cancer Network «www.nccn.org», may help the patient to better accept the process. Many benefit coverage plans cover clinical trials under certain conditions, and the health plan adds value both in its establishing the standards for a national or academic sponsorship of these trials and by making members and physicians aware of the opportunity.

Because of the complexities of breast cancer treatment and the fact that so many options are available at every stage and level of aggressiveness, the treatment map for breast cancer can be circuitous. The resulting care can be fragmented, because it involves numerous clinicians. Medical directors should work to ensure that every breast cancer patient has the services of a trustworthy clinician-guide who can reduce fragmentation and help the patient to navigate the treatment maze.

At numerous points, the breast cancer patient may be uncertain about where she should turn for help or what she should do next. Medical directors should develop programs that facilitate access to reliable consumer-friendly information and serve to activate the woman with breast cancer to take appropriate action.

Today, variation exists in how physicians treat disease. Health plan programs should aim to ensure that the breast cancer patient is informed of the evidence-based options and the benefits and risks of each, and that her personal preferences are taken into account in the decision-making process.

Furthermore, the clinician-guide can help the patient become a better consumer of health care services by teaching her the questions she should ask her treating physicians. For example, in addition to knowing that in many cases breast-conserving surgery and mastectomy have equivalent survival rates, she needs to know that both options are available to her in order to choose between them in accordance with her personal preferences. Likewise, a postmenopausal woman needs to know whether she is eligible for hormone therapy with tamoxifen or an aromatase inhibitor (anastrozole, exemestane, or letrozole).

| TABLE 2 Economic burden of breast cancer among postmenopausal employees |
|-----------------|-----------------|-----------------|-----------------|
|                 | Direct costs    | Indirect costs  | Total           |
| Breast cancer   | $13,925         | $8,236          | $22,161         |
| (n=555)         |                 |                 |                 |
| Cardiovascular  | $12,055         | $4,990          | $17,045         |
| disease (n=1,710)|                 |                 |                 |
| Osteoporosis (n=2,314)| $6,259 | $4,039          | $10,298         |
| Random sample   | $2,951          | $2,292          | $5,243          |
| (n=7,575)       |                 |                 |                 |

SOURCE: SASSER 2005

| FIGURE Estimated number of postmenopausal women in United States, 2005–2015 |
|-------------------------------|-----------------|-----------------|
| In thousands                  | Age 65+         | Age 50–64       |
| 0                             | 100             | 200             | 300             | 400             | 500             | 600             | 700             | 0               | 100             | 200             | 300             |
| 2005                          | 650             | 550             | 450             | 350             | 250             | 150             | 50              | 0               | 100             | 200             | 300             |
| 2006                          | 650             | 550             | 450             | 350             | 250             | 150             | 50              | 0               | 100             | 200             | 300             |
| 2007                          | 650             | 550             | 450             | 350             | 250             | 150             | 50              | 0               | 100             | 200             | 300             |
| 2008                          | 650             | 550             | 450             | 350             | 250             | 150             | 50              | 0               | 100             | 200             | 300             |
| 2009                          | 650             | 550             | 450             | 350             | 250             | 150             | 50              | 0               | 100             | 200             | 300             |
| 2010                          | 650             | 550             | 450             | 350             | 250             | 150             | 50              | 0               | 100             | 200             | 300             |
| 2011                          | 650             | 550             | 450             | 350             | 250             | 150             | 50              | 0               | 100             | 200             | 300             |
| 2012                          | 650             | 550             | 450             | 350             | 250             | 150             | 50              | 0               | 100             | 200             | 300             |
| 2013                          | 650             | 550             | 450             | 350             | 250             | 150             | 50              | 0               | 100             | 200             | 300             |
| 2014                          | 650             | 550             | 450             | 350             | 250             | 150             | 50              | 0               | 100             | 200             | 300             |
| 2015                          | 650             | 550             | 450             | 350             | 250             | 150             | 50              | 0               | 100             | 200             | 300             |

SOURCE: US CENSUS BUREAU 2004
In the presentation of information about any aspect of breast cancer, clinicians should be mindful that patients vary tremendously in their desire for information, and in their ability to process it. An inadequate amount of information for one patient may constitute information overload for another. Moreover, the manner in which information is presented may protect patients against the development of depression or anxiety, or both (Burgess 2005). Simply giving women a choice among surgical options does not protect against depression and anxiety, but communicating with them effectively does.

**Depression and anxiety.** Aside from diminishing quality of life, depression interferes with problem-solving, self-care, and compliance with cancer treatment and may also adversely affect prognosis. (Somerset 2004). About one quarter of breast cancer patients have comorbid depression, in comparison with a prevalence of about 6 percent in the general population (Aapro 1999). In the first year following a diagnosis of early breast cancer, nearly half the women experience depression, anxiety, or both (Burgess 2005). Afterwards, rates of depression and anxiety decline to about 25 percent in years 2 through 4, and to 15 percent in year 5. If breast cancer recurs, however, the prevalence of depression and anxiety may actually exceed the prevalence occurring after the initial diagnosis. Women diagnosed with a recurrence of breast cancer report the same feelings of terror, shock, and disbelief as they did after the initial diagnosis (Payne 1996).

The identification of breast cancer patients with depression is complicated by the fact that many signs and symptoms of depression — such as weight loss, sleep difficulties, and fatigue — coincide with the effects of cancer. Women may have negative psychological reactions to radiation therapy or chemotherapy that need to be recognized and addressed. Self-rating scales such as the Beck Depression Inventory or the Carroll Depression Rating Scale are among the tools that are available for screening for major or minor depression, so that antidepressant therapy can be initiated (Somerset 2004). In addition, many support groups are available to help breast cancer patients and their families through the challenges of the illness and its treatment. This support can be a significant adjunct to the pharmacologic and cognitive treatment of depression.

**REDUCING THE RISK OF RECURRENCE**

Not surprisingly, recurrence of breast cancer is associated with an increase in pain, suffering, mortality, and cost. A retrospective analysis of a cohort of 1,616 women with early breast cancer (stage I and II) in the Henry Ford Health System (a large, vertically integrated Midwestern health care system employing salaried physicians) found that over a median follow-up of 44.5 months, patients with recurrence had a 7.6-fold higher risk of death compared with patients without recurrence, with the hazard ratio varying by site (distant, 13.6; locoregional, 4.5; contralateral breast, 3.0) (Lamerato 2005). Charges for patients with recurrence were substantially higher than those for patients without evidence of recurrence ($157,215 vs. $74,568) (Lamerato 2004). Costs over 6 and 12 months were highest for patients with distant recurrence (Table 3).

Adjuvant hormone therapy is directed at reducing the risk of breast cancer recurrence. Until recently, tamoxifen was standard treatment for women with ER-positive breast cancer, with 1, 2, and 5 years of adjuvant treatment having been shown to reduce the risk of recurrence by 18, 25, and 42 percent, respectively, and the risk of all-cause mortality by 10, 15, and 22 percent in women with early breast cancer (EBCTCG 1998). The benefits of tamoxifen therapy occur predominantly in women with ER-positive tumors, with a 50 percent relative reduction in recurrence and a 28 percent relative reduction in all-cause mortality being reported after 5 years of adjuvant treatment. The benefits of 5 years of adjuvant tamoxifen therapy persist for at least 10 years, with relative reductions in disease recurrence and all-cause mortality being 47 percent and 26 percent, respectively, after 10 years of follow-up. In women with operable breast cancer, however, extending the duration of adjuvant tamoxifen treat-

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>Mean charges before and after breast cancer recurrence in a Midwestern health system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before recurrence</td>
<td>After recurrence</td>
</tr>
<tr>
<td>6 months</td>
<td>12 months</td>
</tr>
<tr>
<td>Overall</td>
<td>$10,715 (n=104)</td>
</tr>
<tr>
<td>Locoregional recurrence</td>
<td>$8,507 (n=35)</td>
</tr>
<tr>
<td>Contralateral breast</td>
<td>$4,788 (n=17)</td>
</tr>
<tr>
<td>Distant recurrence</td>
<td>$14,136 (n=52)</td>
</tr>
</tbody>
</table>

SOURCE: LAMERATO 2004
Table 4: Third-generation aromatase inhibitors

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Anastrozole</th>
<th>Exemestane</th>
<th>Letrozole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade name/manufacturer</td>
<td>ARIMIDEX®/AstraZeneca</td>
<td>AROMASIN®/Pfizer</td>
<td>FEMARA®/Novartis</td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>Nonsteroidal inhibitor (reversible, type II)</td>
<td>Steroidal inactivator (irreversible, type I)</td>
<td>Nonsteroidal inhibitor (reversible, type II)</td>
</tr>
<tr>
<td>Half-life</td>
<td>50 hours</td>
<td>24 hours</td>
<td>48 hours</td>
</tr>
<tr>
<td>Initial US FDA approval</td>
<td>1995 (December)</td>
<td>1999 (October)</td>
<td>1997 (July)</td>
</tr>
<tr>
<td>Route/dosing form (strength)</td>
<td>Oral/tablet (1 mg)</td>
<td>Oral/tablet (25 mg)</td>
<td>Oral/tablet (2.5 mg)</td>
</tr>
<tr>
<td>Indications (all indications are for post-menopausal women)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Treatment of advanced breast cancer that has progressed following tamoxifen therapy</td>
<td>• Treatment of advanced breast cancer that has progressed following treatment with tamoxifen</td>
<td>• Treatment of advanced breast cancer that has progressed following antiestrogen therapy</td>
<td></td>
</tr>
<tr>
<td>• First-line treatment of HR-positive or HR-unknown locally advanced or metastatic breast cancer</td>
<td>• Adjuvant treatment of postmenopausal women with estrogen-receptor positive early breast cancer who have received 2 to 3 years of tamoxifen and are switched to exemestane for completion of a total of 5 years of adjuvant hormonal therapy</td>
<td>• First-line treatment of HR-positive or HR-unknown locally advanced or metastatic breast cancer</td>
<td></td>
</tr>
<tr>
<td>• Adjuvant treatment of HR-positive early breast cancer</td>
<td></td>
<td>• Extended adjuvant treatment of early breast cancer after 5 years of adjuvant tamoxifen therapy</td>
<td></td>
</tr>
</tbody>
</table>

* ARIMIDEX is a registered trademark of the AstraZeneca Group of companies.
† AROMASIN is a registered trademark of Pfizer.
‡ FEMARA is a registered trademark of Novartis Pharmaceuticals.
§ All monthly prices have been calculated from the average wholesale price per tablet, based on prices accessed November 2005 at First DataBank. Comparable monthly price calculated on basis of 30 tablets for tamoxifen 20 mg is $113.77 ($3.79/tablet).”

The benefit beyond 5 years appears to offer no further advantage in patients with ER-positive breast cancer and negative axillary lymph nodes (Fisher 2001).

The third-generation aromatase inhibitors (Table 4), while not yet shown to offer any mortality benefit in comparison with tamoxifen, have been demonstrated to reduce the risk of breast cancer recurrence in women with ER-positive tumors. The American Society of Clinical Oncology has recommended that an aromatase inhibitor be included as adjuvant therapy for such patients, either as initial therapy or subsequent to tamoxifen (Winer 2005).

The benefit from aromatase inhibitors may be a class effect, but as of now, anastrozole is the only one with data...
supporting its use as first-line early adjuvant monother-

apy. After a median follow-up of 68 months, HR-positive

patients treated with anastrozole in ATAC had a 17 per-

cent reduction in the risk of recurrence compared to the
tamoxifen-treated patients (Howell 2005). In the HR-
positive patients, the absolute difference in time to re-
currence, in favor of anastrozole, was 1.7 and 3.7 percent
after 3 and 6 years, respectively.

The aromatase inhibitors offer adverse-event profiles
different from that of tamoxifen. In the ATAC (Arimi-
dex, Tamoxifen, Alone or in Combination) trial, with 68
months of follow-up, in addition to tamoxifen, pa-
tients who were receiving anastrozole were less likely to
experience endometrial cancer (odds ratio [OR], 0.20),
ischemic cerebrovascular disease (OR, 0.70), venous
thrombotic events (OR, 0.61), deep vein thrombosis
(OR, 0.64), hot flashes (OR, 0.80), vaginal bleeding (OR,
0.50) and vaginal discharge (OR, 0.24) but they were
more likely to experience fractures (OR, 1.49) and
arthralgia (OR, 1.32) (Howell 2005).

As they weigh the risks versus benefits of hormonal therapies from their different perspectives, medical on-
cologists and primary care physicians occasionally may
find themselves in disagreement about which agent or
combination of agents is best for a given patient. In such
instances, the medical director may be able to mediate a
resolution, perhaps by simply reminding the physicians
of the importance of placing the patient’s informed pref-

ferences in the forefront of their professional recom-

mendations.

VARIATIONS IN TREATMENT

A distressing trend in medical care in the United States
is the increasing disparity in breast cancer death rates be-
tween white and African-American women. As recently
as 1981, the age-adjusted death rates for both groups were
equally equal (about 31 per 100,000), but since then, a gap has developed and widened, to the extent that,
by 2000, the excess deaths among African-Americans
were more than 30 percent greater than those among white women (ACS 2003). This difference, a serious pub-
lic health problem, is explained more by socioeconomic
factors than by any biological characteristics; equal treat-
ment should lead to equal outcomes (Shavers 2002).
Medical directors need to take a close look at the sub-
populations served by their health plans to make sure that
the same level of treatment is extended to every patient,
and that screening is used appropriately to diagnose
breast cancer at an early stage. They may need to consider
culturally sensitive and focused communication and
messaging.

Possibly reflecting uncertainty about the value of
mammography owing to conflicting recommendations,
rates of mammography have reached a plateau among all
types of MCOs (NCQA 2004). In commercial and Medi-
care plans, breast cancer screening rates have hovered
around 75 percent for the past 4 years, while in Med-
icaid plans the rate has been no greater than 56 percent
during this period. This HEDIS measure estimates the
percentage of women ages 52 to 69 who had at least
1 mammogram in the previous 2 years. Medical directors
can encourage their health plans to improve their per-
formance in this HEDIS measure, and to make sure
mammography rates are consistent across subgroups
within the health plan.

CONCLUSION

By virtue of their leadership positions, medical direc-
tors are capable of substantially lessening the burden
that is imposed by breast cancer on their health plans and
on individual members. It is incumbent on medical di-
rectors to adopt a consumer-oriented, culturally sensitive
approach to early breast cancer, focusing on the issues
that are important to the patient. As more is learned
about the way individuals respond to stress, cope with
chronic conditions, and approach significant decision
making, the health plan can play a central role in shar-
ing these insights with their members and their network
physicians. Emphasis should be placed on early diagno-
sis, sensitivity to the patient’s wide range of emotions, ap-
propriate treatment that conforms with the patient’s
preferences, and efforts to reduce the risk of disease re-
currence.

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