CANCER MANAGEMENT: 13TH EDITION

Breast Cancer Overview: Risk Factors, Screening, Genetic Testing, and Prevention

By Lori Jardines, MD1, Sharad Goyal, MD2, Paul Fisher, MD3, Jeffrey Weitzel, MD4, Melanie Royce, MD, PhD5, Shari B. Goldfarb, MD6 | 2011t325â

1 Division of Surgery, Albert Einstein Medical Center
2 Department of Radiation Oncology, Robert Wood Johnson Medical School, The Cancer Institute of New Jersey
3 Department of Radiology and Surgery, Stony Brook University Medical Center
4 Division of Clinical Cancer Genetics, City of Hope National Medical Center
5 Division of Hematology/Oncology, University of New Mexico Cancer Center
6 Breast Cancer Medicine Service, Memorial Sloan-Kettering Cancer Center

Breast cancer is the most common malignancy in women, accounting for 27% of all female cancers; it accounts for < 1% of all cancer cases in men. Breast cancer also is responsible for 15% of cancer deaths in women, making it the number-two cause of cancer death. An estimated 207,090 new breast cancer cases will be diagnosed in women and 1,970 new cases will be diagnosed in men in the United States in 2010, and 39,840 women and 390 men will die of this cancer. As of 2010, there are approximately 2.9 million breast cancer survivors in the United States.

This chapter provides an overview of breast cancer, with discussions of epidemiology, etiology and risk factors, genetic cancer risk assessment, signs and symptoms, screening and diagnosis, prevention (including lifestyle changes and chemoprevention), staging, and prognosis. The three chapters that follow focus on the management of stages 0 and I, stage II, and stages III and IV breast cancers.

epidemiology

Gender
Breast cancer is relatively uncommon in men; the female-to-male ratio is approximately 100:1. The incidence of breast cancer in men has remained relatively stable over the past decades, except in Africa, where, for unclear reasons, the incidence is rising. BRCA mutations are associated with an increased risk for breast cancer in men.
The most common presentations of breast cancer in men are asymmetric gynecomastia or a palpable mass. All palpable masses in men should be carefully examined. Based upon the findings on physical examination, mammography and breast ultrasonography should be considered. Fine-needle aspiration (FNA) or core biopsy can be used to distinguish between gynecomastia and breast cancer. Core biopsy may be performed if the FNA is nondiagnostic.

Age
The risk of developing breast cancer increases with age. The disease is uncommon in women younger than 40 years of age; only about 0.8% of breast cancers occur in women < 30 years old, and approximately 6.5% develop in women between 30 and 40 years old.

Race
Caucasian women have a higher overall rate of breast cancer than do African-American women; however, this difference is not apparent until age 50 and is marked only after menopause. In the United States, the incidence of breast cancer in Asian and Hispanic women is approximately half that in white women. Breast cancer risk is extremely low in Native-American women.

Geography
There is at least a fivefold variation in the incidence of breast cancer reported in different countries, although this difference appears to be narrowing. The incidence of breast cancer is significantly lower in Japan, Thailand, Nigeria, and India than in Denmark, the Netherlands, New Zealand, Switzerland, the United Kingdom, and the United States. Women living in North America have the highest rate of breast cancer in the world. It has been suggested that these trends in breast cancer incidence somehow may be related to dietary influences, particularly dietary fat consumption (see section on "Etiology and risk factors").

Socioeconomic status
The incidence of breast cancer is higher in women of higher socioeconomic background. This relationship is most likely related to lifestyle differences, such as age at first birth and dietary fat intake.

Disease site
The left breast is involved slightly more frequently than the right, and the most common locations of the disease are the upper outer quadrant and retroareolar region. The risk of contralateral breast cancer in women with a mutation of a breast cancer gene (BRCA) is approximately 40% at 10 years after the initial diagnosis of breast cancer. This risk is higher in BRCA1 than BRCA2 mutation carriers and in those first diagnosed at age < 50.

Risk for breast cancer is reduced in women who take tamoxifen. Bilateral salpingo-oophorectomy (BSO) also reduces breast cancer risk, especially when this procedure is performed in women younger than age 50. The protective effect of BSO is pronounced among women who develop breast cancer premenopausally.

Survival
Survival rates for patients with nonmetastatic breast cancer have improved in recent years (Table 1). These improvements may be secondary to advances in screening, adjuvant chemotherapy, and radiation.
therapy. The contribution of screening mammography to breast cancer-specific survival is variable, favoring a reduction in breast cancer mortality of up to 25% in some series. Its impact on overall survival is less certain.

**Etiology and risk factors**

The development of breast cancer has been associated with numerous risk factors, including genetic, environmental, hormonal, and nutritional influences. Despite all of the available data on breast cancer risk factors, 75% of women with this cancer have no risk factors.

**Genetic factors**

Hereditary forms of breast cancer constitute only 5% to 10% of breast cancer cases overall. However, the magnitude of the probability that a woman will develop cancer if she inherits a highly penetrant cancer gene mutation justifies the intense interest in predictive testing. Commercial testing is available for several genes (BRCA1, BRCA2, tumor protein p53 gene [TP53]) associated with a high risk for breast cancer development.

Elevated risk for breast cancer is also associated with mutations in the PTEN gene in Cowden's syndrome (described later). In addition, a modest increased risk (relative risk of RR = 3.9-6.4) may be seen in women who are heterozygous for a mutation in the ATM gene, ataxia telangiectasia mutated gene (ATM), which is associated with the recessive disease ataxia-telangiectasia in the homozygous state. A moderately increased risk for breast cancer (2-fold for women and 10-fold for men) has also been associated with a variant (1100 delC) in the cell-cycle checkpoint kinase gene, CHEK2.

**BRCA1 gene**

The BRCA1 gene is located on chromosome 17. This gene is extremely large and complex, and there are more than 1,000 different possible mutations. BRCA1 mutations are inherited in an autosomal-dominant fashion and are associated with an increased risk for breast, ovarian, and, to a lesser degree, prostate cancers. A BRCA1 mutation carrier has a 56% to 85% lifetime risk of developing breast cancer and a 15% to 45% lifetime risk of developing ovarian cancer.

**BRCA2 gene**

The BRCA2 gene was localized to chromosome 13. BRCA2 is approximately twice as large as BRCA1 and is similarly complex.

Alterations in BRCA2 have been associated with an increased incidence of breast cancer in both women (similar to BRCA1) and men (6% lifetime risk). BRCA2 mutations are also associated with an increased risk for ovarian cancer, pancreatic cancer, prostate cancer, and melanoma. Together, mutations of BRCA1 and BRCA2 have been linked to most hereditary breast and ovarian cancer families and approximately half of hereditary breast cancer families.

The incidence of BRCA gene mutations in the general breast cancer population is unknown, since most of the data have come from studies of high-risk populations. In one population-based study of women with breast cancer, 9.4% of women < 35 years of age at the time of diagnosis and 12.0% of women < 45 years old who also had a first-degree relative with breast cancer had germline BRCA1 or BRCA2 mutations. However, a 40-year-old woman of Ashkenazi Jewish ancestry who has breast cancer has a 20% to 30% probability of bearing one of three founder BRCA gene mutations, based on data from high-risk clinics, testing vendors, and Israeli series.
**Li-Fraumeni syndrome**
This rare syndrome is characterized by premenopausal breast cancer in combination with childhood sarcoma, brain tumors, leukemia, and adrenocortical carcinoma. Tumors frequently occur in childhood and early adulthood and often present as multiple primaries in the same individual. Germline mutations in the \( TP53 \) gene on chromosome 17p have been documented in persons with this syndrome. Inheritance is autosomal dominant, with a penetrance of at least 50% by age 50. Although the rarity of this syndrome, the diversity of tumor types, and the fact that the age of patients at risk spans from childhood to young adulthood makes coherent screening strategies beyond those for the early-onset breast cancer risk difficult to find, a recent pilot study with 18-fluorodeoxyglucose positron emission tomography/CT scanning was promising.

Gonzalez et al recently reported on the largest experience with clinical \( TP53 \) testing published thus far. In all, 91 of 525 patients had a deleterious mutation. The investigators derived user-friendly mutation-probability tables based upon presenting features of individuals and families, with the highest yield noted among children with choroid plexus tumors. The discovery of \( TP53 \) mutations in \( BRCA \)-negative women diagnosed with breast cancer under 30 years old was cited in the 2009 NCCN guidelines (Gonzalez KD et al: J Clin Oncol 27:1250-1256, 2009).

**Cowden’s syndrome**
This syndrome is inherited as an autosomal-dominant trait and is notable for a distinctive skin lesion (trichilemmoma) and mucocutaneous lesions. Patients with this uncommon syndrome have a high incidence of gastrointestinal polyps and thyroid disorders; lifetime estimates for breast cancer among women with this syndrome range from 25% to 50%. Germline mutations in the \( PTEN \) gene, located on chromosome 10q23, are responsible for this syndrome.

**Family history**
The overall RR of breast cancer in a woman with a positive family history in a first-degree relative (mother, daughter, or sister) is 1.7. Premenopausal onset of the disease in a first-degree relative is associated with a threefold increase in breast cancer risk, whereas postmenopausal diagnosis increases the RR by only 1.5. When the first-degree relative has bilateral disease, there is a fivefold increase in risk. The RR for a woman whose first-degree relative developed bilateral breast cancer prior to menopause is nearly 9.

**Proliferative breast disease**
The diagnosis of certain conditions on a breast biopsy is also associated with an increased risk for the subsequent development of invasive breast cancer. They include moderate or florid ductal hyperplasia and sclerosing adenosis, which pose only a slightly increased risk of breast cancer (1.5-2.0 times); atypical ductal or lobular hyperplasia, which moderately increases risk (4-5 times); and lobular carcinoma in situ (LCIS), which markedly increases risk (8-11 times; see more detailed discussion of LCIS in chapter 6). Patients who have a family history of breast cancer along with a personal history of atypical epithelial hyperplasia have an eightfold increase in breast cancer risk when compared with patients with a positive family history alone and an 11-fold increase in breast cancer risk when compared with patients who do not have atypical hyperplasia and have a negative family history.

**Personal cancer history**
A personal history of breast cancer is a significant risk factor for the subsequent development of a second, new primary breast cancer. This risk has been estimated to be as high as 1% per year from the time of diagnosis of an initial sporadic breast cancer. Women with \( BRCA \)-associated cancer have a 3% to 5% per year risk of contralateral breast cancer (cumulative lifetime risk of up to 64% in high-risk cohorts). Women with a history of endometrial, ovarian, or colon cancer also have a higher likelihood of developing breast cancer than do those with no history of these malignancies.
Menstrual and reproductive factors
Early onset of menarche (< 12 years old) has been associated with a modest increase in breast cancer risk (twofold or less). Women who undergo menopause before age 30 have a twofold reduction in breast cancer risk when compared with women who undergo menopause after age 55. A first full-term pregnancy before age 30 appears to have a protective effect against breast cancer, whereas a late first full-term pregnancy or nulliparity may be associated with a higher risk. There is also a suggestion that lactation protects against breast cancer development.

Radiation exposure
An increased rate of breast cancer has been observed in survivors of the atomic bomb explosions in Japan, with a peak latency period of 15 to 20 years. More recently, it has been noted that patients with Hodgkin lymphoma who are treated with mantle irradiation, particularly women who are younger than age 20 at the time of radiation therapy, have an increased incidence of breast cancer.

Exogenous hormone use
In regard to hormone replacement therapy (HRT) or postmenopausal hormone use, results from the WHI showed that the overall risks of estrogen plus progestin outweigh the benefits. This large randomized clinical trial sponsored by the NIH included more than 16,000 healthy women. Results from the WHI trial were published in 2002, after an average 5.6 years of follow-up, and included a 26% increase in risk of invasive breast cancer among women taking estrogen plus progestin, as compared with women taking placebo. In addition, in women taking these hormones, there were increased risks of heart disease, stroke, and blood clots.

The NIH stopped the estrogen-alone arm of the WHI trial in March 2004. No increase in breast cancer risk was observed in the estrogen-alone arm during the study period (7 years of follow-up). The NIH concluded that estrogen alone does not appear to increase or decrease a woman’s risk of heart disease, although it does appear to increase her risk of stroke and decrease her risk of hip fracture.

Following the publication of the WHI trial results, the use of HRT in the United States declined by almost 40% from 2002 to 2003. During approximately the same period, there was a 6.7% decline in the age-adjusted incidence of breast cancer. Furthermore, the decrease was evident only among women 50 years of age and older and primarily among those with estrogen receptor-positive breast cancers.

Alcohol
Moderate alcohol intake (two or more drinks per day) appears to modestly increase breast cancer risk.

High-fat diet
Diets that are high in fat have been associated with an increased risk for breast cancer. Women who have diets high in animal fat from high-fat dairy foods have an increased risk of developing breast cancer. Whether the increase in breast cancer risk is associated with the fat content or an unknown carcinogen in these foods is unclear. There is no association between the consumption of red meat and an increased risk of breast cancer.

Obesity
Alterations in endogenous estrogen levels secondary to obesity may enhance breast cancer risk. Obesity appears to be a factor primarily in postmenopausal women.

In late 2007, the RRs of cancer incidence and mortality from the Million Women Study were reported. The study analyzed data on 1.2 million women in the UK (age from 1996-2001, 50-64 years) who were followed for an average of 5.4 years for cancer incidence and 7.0 years for cancer mortality. In all, 45,037 incident cancers and 17,203 deaths from the disease occurred during follow-up. An increased
incidence of breast cancer with increasing body mass index (BMI) was noted. For breast cancer, the effect of BMI on risk differed significantly according to menopausal status (RR in postmenopausal women = 1.40). Calculations were adjusted for BMI, age, geographic region, socioeconomic status, age at first birth, parity, smoking status, alcohol use, physical activity, years since menopause, and use of HRT.

Genetic cancer risk assessment

Genetic testing clearly has the potential to benefit carefully selected and counseled families. Education and adequately trained health care professionals are key elements in the successful integration of genetic cancer risk assessment into clinical practice.

The genetic risk assessment process begins with an evaluation of perceived risk and the impact of cancer on the patient and family. This information forms the framework for counseling.

Comprehensive personal and family histories
Detailed information regarding personal, reproductive, and hormonal risk factors is noted. Family history, including age at disease onset, types of cancer, and current age or age at death, is obtained for all family members going back at least three generations.

Documentation of cancer cases
Documentation is crucial to accurate risk estimation. Pathology reports, medical record notes, and death certificates may all be used in determining the exact diagnosis.

Pedigree construction and evaluation
The family pedigree is then constructed and analyzed to determine whether a pattern of cancer in the family is consistent with genetic disease. Sometimes, small family structure or lack of information about the family limits assessment of a hereditary trait; other times, clues such as ancestry or early age at diagnosis influence risk assessment and the usefulness of genetic testing.

Individual risk assessment
Several models are used to estimate the likelihood that a detectable \textit{BRCA1} or \textit{BRCA2} mutation is responsible for the disease in the family. The \textit{BRCA PRO} computer program is a cancer risk-assessment tool that uses a family history of breast or ovarian cancer in first- and second-degree relatives to calculate the probabilities that either a \textit{BRCA1} or \textit{BRCA2} mutation is responsible for the disease. It includes a Bayesian calculation (of conditional probability) to account for age-specific penetrance differences. If genetic testing is not performed or results are uninformative, the empirical breast cancer risk is estimated by the phenotype as well as the Claus model (derived from the Cancer and Hormone Study, which uses age at onset of breast cancer among first- and second-degree relatives) or Gail model. Personal and family characteristics that are associated with an increased likelihood of a \textit{BRCA1} or \textit{BRCA2} mutation are summarized in Table 2.

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Features indicating an increased likelihood of a BRCA mutation \\
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Cancer and Hormone Study, which uses age at onset of breast cancer among first- and second-degree relatives) or Gail model. Personal and family characteristics that are associated with an increased likelihood of a BRCA1 or BRCA2 mutation are summarized in Table 2.

**Education**

Patients should be given information about the principles of genetics and hereditary cancer patterns and the application of genetic testing (appropriateness, limitations, advantages, and disadvantages).

**Genetic counseling and testing**

Informed consent is obtained before genetic testing is performed. For individuals who decide to undergo testing, a post-test counseling session is scheduled to disclose and explain the results in person.

### Table 2

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### Table 3

**Risk management options for BRCA mutation carriers**

**Customized screening and prevention recommendations**

Regardless of whether or not a woman undergoes genetic testing, a customized management plan is delineated, with the goal of preventing or detecting malignancy early, within the context of the patient's personal preferences and degree of risk (Table 3).

### Laboratory methods

Several techniques/strategies for detecting mutations in cancer genes have been adopted by different researchers and commercial vendors.

Directed assays are available for specific founder or ancestral mutations that are common in a given population. Among Ashkenazi Jews, 1 in 40 individuals bears one of three founder mutations (185delAG and 5382insC in **BRCA1** and 6174delT in **BRCA2**); these mutations account for 25% of early-onset breast cancer in this population. Moreover, 95% of Ashkenazi Jews with a **BRCA** gene mutation will have one of the three founder mutations. However, complete gene sequencing can be performed if a patient does not test positive for a founder mutation.

The lifetime risk of breast cancer was 82% among founder mutation carriers in a large cohort of Jewish families identified via a New York breast cancer study. The lifetime risk of ovarian cancer was 54% for **BRCA1** and 23% for **BRCA2**, similar to the risk in multiplex families from the BCLC. However, a population-based study indicated a lifetime breast cancer risk of 40% to 73%.

**Limitations**

All of the approaches to detecting mutations have limitations. In general, discovery of an inactivating or "deleterious" mutation of either **BRCA1** or **BRCA2** indicates a high probability that a person will develop breast and/or ovarian cancer.

One of the greatest challenges is the interpretation of missense mutations. These mutations are more likely to be significant if located in an evolutionarily conserved or functionally critical region of the protein. In the absence of a clear disease association, it is often difficult to exclude the possibility that a
given missense alteration simply represents a rare polymorphism. Using advanced methods, a recent study was able to characterize 133/1,433 variants as likely polymorphisms and 43 as likely deleterious; the majority would still be designated as "genetic variants of uncertain significance."

Although less common, mutations in other genes besides BRCA1 and BRCA2 (eg, CHEK2 and TP53) may predispose patients to breast cancer. Walsh et al demonstrated inherited genomic rearrangements of BRCA1 and BRCA2 in 35 of 300 (12%) sequence-negative, high-risk families. They also highlighted other single-gene breast cancer predisposition traits in a subset of families (eg, 14 with a CHEK2 mutation and 3 with a TP53 mutation). In part, this finding prompted accelerated implementation of a commercial screen.

**Testing strategies**
In general, testing should be initiated with the youngest affected individual in a given family. Even if one is convinced that a family has hereditary breast and ovarian cancers based on clinical criteria, there is only a 50% chance that an offspring or sibling of an affected patient will have inherited the deleterious allele. Therefore, only a positive test result (detection of a known or likely deleterious mutation) is truly informative.

Until the "familial mutation" is known, a negative test result could mean either that the unaffected person being tested did not inherit the cancer susceptibility mutation or that the person inherited the disease-associated gene, but the mutation was not detectable by the methods used.

In many cases, no affected family members are available for testing. In that case, one may proceed with genetic testing of an unaffected person, but only after that individual has been thoroughly counseled regarding its risks, benefits, and limitations.

Unless there is a suggestive family history, cancer susceptibility testing is not considered appropriate for screening unaffected individuals in the general population. However, it may be reasonable to test unaffected persons who are members of an ethnic group in which specific ancestral mutations are prevalent and whose family structure is limited (ie, the family is small, with few female relatives or no information due to premature death from noncancerous causes).

**Impact of genetic cancer risk status on management**
Data from the BCLC suggest that the cumulative risk of developing a second primary breast cancer is approximately 65% by age 70 among BRCA gene mutation carriers who have already had breast cancer. A large, retrospective cohort study of BRCA mutation carriers with a history of limited-stage breast cancer indicated up to a 40% risk of contralateral breast cancer at 10 years. A subsequent study of the same cohort noted almost a 13% risk for ovarian cancer in the same interval and that ovarian cancer was the cause of cancer death in 25% of stage I breast cancer patients with BRCA mutations.

Thus, knowledge of the genetic status of a woman affected with breast cancer might influence the initial surgical approach (eg, bilateral mastectomy might be recommended for a mutation carrier instead of a more conservative procedure). Moreover, since ovarian cancer risk may be markedly increased in women with BRCA1 mutations (and to a lesser degree with BRCA2 mutations), additional measures, such as surveillance for presymptomatic detection of early-stage tumors or consideration of oophorectomy, may be warranted.

According to data from BRCA mutated carriers who underwent risk-reduction salpingo-oophorectomy (RRSO), breast cancer risk is also decreased from bilateral oophorectomies.
Kauff et al reported their findings of a multicenter prospective analysis of RRSO to prevent BRCA-associated breast and ovarian cancers. During a median follow-up of 40 months, RRSO was associated with a 52% reduction in breast cancer risk and a 91% reduction in ovarian cancer risk, with the greatest risk reduction occurring in women with the BRCA2 gene mutation. A total of 886 female BRCA1 or BRCA2 mutation carriers older than age 30 were enrolled from 1 of 11 study centers between 1994 and 2004. Women were treated with either ovarian surveillance (n = 325) or RRSO (n = 561). The investigators believe their results confirm that RRSO is highly protective against BRCA-associated breast and ovarian cancers.

Rebbeck et al performed a meta-analysis of published studies of RRSO in BRCA mutation carriers and confirmed the magnitude of breast cancer risk reduction associated with the procedure. Critically, their findings firmly established a significant risk reduction of BRCA1 carriers (HR = 0.49; 95% CI = 0.35-0.64), who are predisposed to ER-negative tumors in particular (Rebbeck TR et al: J Natl Cancer Inst 101:80-87, 2009).

Both retrospective and prospective data have demonstrated the efficacy (> 90% risk reduction) of bilateral mastectomy in women who are at high risk for the disease based upon BRCA genetic status. Women who opt for risk-reduction mastectomy should be offered reconstruction. Skin-sparing mastectomy may enhance the cosmetic results of reconstruction and should be discussed with the patient's surgeon. This procedure entails removing the breast tissue (including the nipple-areolar complex).

The efficacy of bilateral risk-reduction mastectomy has been confirmed in a large prospective study of 483 women with BRCA mutations. With a mean follow-up of 6.4 years, risk reduction mastectomy reduced the risk of breast cancer by 90% (95% in women who also underwent RRSO).

Data presented at ASCO in 2008 and 2009 suggested that a "synthetic lethality" strategy involving treatment with poly (ADP-ribose) polymerase (PARP) inhibitors is effective in women with BRCA-associated breast or ovarian cancer.

**Potential benefits and risks of genetic testing**

The ability to identify individuals at highest risk for cancer holds the promise of improved prevention and early detection of cancers. Patients who are not at high risk can be spared anxiety and the need for increased surveillance. Recent studies suggest a better emotional state among at-risk relatives who undergo testing than among those who choose not to know their status. The patient's perception of risk is often much higher than risk estimated by current models.

**Potential risks**

Potential medical, psychological, and socioeconomic risks must be addressed in the context of obtaining informed consent for genetic testing.

**Concerns about insurance**

Fear about adverse effects of testing on insurability remains the premier concern among patients. Close behind that is concern about the cost of analyzing large complex genes ($3,600 for full sequencing of BRCA1 and BRCA2 and an additional $800 if the test for genomic rearrangements is ordered a la carte).

**Legal and privacy issues**

The legal and privacy issues surrounding genetic testing are as complex as the testing technologies. Although several state laws regarding the privacy of medical information, genetic testing, and insurance and employment discrimination have been passed, they vary widely.
The 1996 Health Insurance Portability and Accountability Act (US public law 104-191), governing group medical plans, stipulates that genetic information may not be treated as a preexisting condition in the absence of a diagnosis of the condition related to such information. It further prohibits basing rules for eligibility or costs for coverage on genetic information. However, the law did not address genetic privacy issues and does not cover individual policies. Many states have laws addressing genetic discrimination, but concerns about gaps remained. Recent Federal legislation expanded protection against genetic discrimination to include individual policies. The Genetic Information Nondiscrimination Act of 2008 (GINA) prohibits health insurers and employers from discriminating against individuals on the basis of genetic information.

Data from recent clinical trials suggested that poly (ADP-ribose) polymerase (PARP) inhibitors show promising antitumor effects as single agents in BRCA-associated breast and ovarian cancer (Fong PC et al: N Engl J Med 361:1-12, 2009).

**Recommendations for genetic testing**

Guidelines from ASCO recommend that cancer predisposition testing be offered only in the following situations: (1) if a person has a strong family history of cancer or early onset of disease; (2) if the test can be adequately interpreted; and (3) if the results will influence the medical management of the patient or family member.

NCCN practice guidelines for genetics/familial high-risk cancer screening are updated annually and published at www.nccn.org.

ASCO recently presented an update of its policy statement regarding genetic testing to extend commentary on the lack of documented clinical utility of commercially available genomic tests relying on single nucleotide polymorphism markers with very modest relative risk for breast cancer (Robson ME et al: J Clin Oncol 28:893-901, 2010)

Weitzel et al characterized the impact of family structure on the prevalence of BRCA gene mutations among 306 women who developed breast cancer before the age of 50 years and who had no first- or second-degree relatives with breast or ovarian cancer. BRCA mutations were detected in 13.7% of women with limited family structure (ie, fewer than two first- or second-degree relatives surviving beyond age 45 years in either lineage) and 5.2% of those having adequate family structure. Family structure, therefore, apparently is a strong predictor of mutation status (odds ratio = 2.8; 95% confidence interval = 1.19-6.73, \(P = .019\)). Genetic testing guidelines may need to be more inclusive for single cases of breast cancer when family structure is limited.

**Signs and symptoms**

**Mammographic findings**

Increasing numbers of breast malignancies are being discovered in asymptomatic patients through the use of screening mammography. Mammographic features suggestive of malignancy include asymmetry, microcalcifications, a mass, or an architectural distortion.

When these features are identified on a screening mammogram (see Figures 1-5), they should, in most cases, be further evaluated with a diagnostic mammogram (and, in some cases, with a breast ultrasonographic image or, in highly selected cases, with MRI [Figure 6]) prior to determining the need for a tissue diagnosis. Often, pseudolesions, such as those caused by a summation artifact, dust on the mammographic cassettes, and dermal...
calcifications, are correctly identified in this manner. All mammographic lesions (and the examinations themselves) must be unambiguously categorized according to one of the six Breast Imaging Reporting Data System (BI-RAD) classifications developed by the ACR (Table 4).

| Table 4: BI-RAD classification of mammographic lesions |

**Breast lump**
When signs or symptoms are present, the most common presenting complaint is a lump within the breast. The incidence of this complaint can range from 65% to 76%, depending on the study.

Inflammatory breast cancer is particularly aggressive, although relatively uncommon, accounting for about 5% of all breast cancers. On breast palpation, there often is no definite mass, but the breast appears to be engorged with erythema, skin edema (peau d'orange), and skin ridging. A short trial of antibiotics or, on rare occasions, ultrasonography may be helpful in differentiating mastitis from inflammatory breast cancer.

**Paget’s disease**
This condition has been associated with intraductal carcinoma involving the terminal ducts of the breasts and may have an associated invasive component. It presents as an eczematoid change in the nipple, a breast mass, or bloody nipple discharge. Cytology may be helpful in establishing the diagnosis; however, negative cytologic results should not preclude a biopsy.

**Other local symptoms**
Breast pain is the presenting symptom in ~5% of patients; breast enlargement, in 1%; skin or nipple retraction, in ~5%; nipple discharge, in ~2%; and nipple crusting or erosion, in 1%.

**Screening and diagnosis**

**Screening**

**Breast self-examination**
The role of breast self-examination is controversial. ACS recommends that beginning in their 20s, women should be instructed in the technique and informed about both the benefits and limitations of this screening tool. Other groups have suggested that routine breast self-examination may lead to more false-positive results and therefore more benign biopsies. One meta-analysis of 12 studies involving a total of 8,118 patients with breast cancer correlated the performance of breast self-examination with tumor size and regional lymph node status. Women who performed breast self-examination were more likely to have smaller tumors and less likely to have axillary node metastases than those who did not. A multicenter study from MSKCC and the University of Virginia attempted to measure the benefits and costs of adding clinical breast exams to yearly screening mammography. These exams detected an additional 14 breast cancers, or 0.02% of the 60,027 exams performed, and the cost for each additional cancer detected was $122,598. Based on this report, the benefit of clinical breast exams appear to be marginal.
A major problem with breast self-examination as a screening technique is that it is rarely performed well. Only 2% to 3% of women do an ideal examination a year after instruction has been provided.

FIGURE 1 Malignant calcifications (comedocarcinoma) in a classic linear dot and dash configuration (BI-RAD 5 lesion). BI-RAD = Breast Imaging Reporting Data System.

FIGURE 2 Left panel: A dense mass with partially unsharp margins (BI-RAD 4 lesion), which proved to be a fibroadenoma. Right panel: A small, spiculated mass (BI-RAD 5 lesion), which has engulfed a coarse, benign calcification.

FIGURE 3 Left panel: This focal mass with truly nonsharp margins (BI-RAD 4 lesion) was diagnosed as a tubular carcinoma on stereotactic core biopsy. Right panel: A well-circumscribed lesion containing fat (BI-RAD 2 lesion), which is pathognomonic for a breast hamartoma (fibroadenolipoma). 

FIGURE 4 Focal architectural distortion may be difficult to see, but, if confirmed, it has the highest positive predictive value for breast carcinoma. This BI-RAD 4 lesion proved to be an invasive lobular carcinoma, which often has a subtle mammographic appearance.

FIGURE 5 This breast ultrasonographic image demonstrates a hypoechoic, solid mass, which exhibits posterior shadowing and is taller than wide. This BI-RAD 4 lesion proved to be an invasive ductal carcinoma, not otherwise specified.
A 42-year-old woman presents with axillary adenopathy, which was positive on fine-needle aspiration. Results of a clinical breast exam, mammography, and ultrasonography were normal. A 7-mm enhancing cancer is clearly seen on this MRI of the breast.

**Clinical breast examination**
The American Cancer Society no longer recommends monthly self-breast examinations. However, all women should learn about the potential benefits, limitations, and harms (false positive results) of breast self-examinations. Women should receive instructions regarding proper technique for breast self-exams and then individually may choose to perform them monthly, occasionally, or never. Beginning at age 40, the clinical breast examination should be timed to occur near or prior to screening mammography. If the clinician detects an abnormality, the patient should then undergo diagnostic imaging rather than screening. Clinical breast examination should be performed and a complete breast history obtained when a woman presents for routine health care. The clinical examination should include inspection and palpation of the breast and regional lymph nodes. Between 14% and 21% of breast cancers are detected by clinical breast examination.

**Mammography**
Despite conflicting coverage in the lay press, the benefits of screening mammography have been well established by the findings of 11 large-scale evidence-based clinical trials. The ACS, the ACR, and the AMA have updated their guidelines since 1997 and recommend annual mammography beginning at age 40. The NCI also updated its guidelines in 1997, recommending that women undergo screening mammography every 1 to 2 years beginning in their 40s. The US Preventive Services Task Force (USPSTF) updated its guidelines and now recommends mammography every 1 to 2 years, alone or with clinical breast examination, for women aged 40 and older.

**Screening mammography**
Screening mammography is performed in the asymptomatic patient to detect an occult breast cancer. This contrasts with diagnostic mammography, which is performed in a patient with a breast abnormality (palpable mass, bloody nipple discharge, or some other clinical finding) to further identify the etiology of the problem.

Physical examination and mammography are complementary. Mammography has a sensitivity of 85% to 90% and, thus, would miss 10% to 15% of clinically evident tumors while detecting the majority of cases an average of 2 years prior to any perceptible clinical signs or symptoms.
Screening recommendations for average-risk patients

No upper age limit has been suggested, and screening should continue in women who are in good health and would be candidates for breast cancer treatment. The previous recommendation for a "baseline" mammogram between the ages of 35 and 40 has been withdrawn. Thus, both the ACS and the NCCN recommend annual mammography starting at age 40 for women at average risk of breast cancer. The USPSTF currently recommends yearly screening mammograms starting at age 50.

Screening recommendations for high-risk patients

Based on epidemiologic evidence that premenopausal familial breast cancer often presents at similar ages among affected family members, many breast imaging centers recommend that yearly screening for such high-risk individuals begin approximately 10 years prior to the youngest age at which a first-degree relative was diagnosed with breast cancer. For example, according to this algorithm, a woman whose mother developed breast cancer at age 45 could begin yearly screening at age 35, in addition to biannual clinical breast examinations. These commonly used screening algorithms are not based on formal studies but have arisen based on the natural history of the disease. They are, however, in keeping with the recommendations of the NCCN guidelines. Screening for women at genetic risk may begin at age 25. There are numerous studies supporting the use of breast MRI in women at genetic risk, all of which indicated that sensitivity is > 80%.

Digital mammography

Digital mammography was approved by the FDA in 2000 and is rapidly being adopted by leading breast cancer centers worldwide. Initial trials indicate a comparable sensitivity to film-based mammography, with the benefit of a reduced risk of women called back from screening for additional workup. The FDA also approved computer-aided detection systems for mammography beginning in 2001. Mammograms are scanned by a computer, and possible lesions are marked for further review by a radiologist. A number of studies have shown a reduced risk of "missed cancers" when computer-aided diagnosis is thus employed. Although some physicians are skeptical about the benefits of such computer-aided detection systems for mammography, many investigators in the field continue to support its use. For example, Lindfors et al published data showing that these systems increased the effectiveness of mammographic screening by 29%, with a comparable increase in screening cost.

Screening ultrasonography

Sensitivity of mammography is diminished when the breast tissue is dense. There have been recent reports in the literature concerning the role of screening breast ultrasonography in women with dense breasts on mammography and normal mammography and clinical breast examination. The results from a multicenter trial of leading breast imagers (ACRIN 6666) showed that the addition of ultrasound to mammography increased detection of breast cancer when compared with mammography alone among women at increased risk of breast cancer who also had dense breast tissue. However, there was also an increase in the number of benign biopsies.

Pending further investigation, screening ultrasonography of the breast is not sanctioned or approved, and, unlike high-risk MRI screening, it does not constitute standard of care. Screening breast ultrasound may have some value in high-risk women with dense breast tissue on mammography, however; it is currently available at some institutions and can be offered to women who meet the aforementioned criteria.

Magnetic resonance imaging

This diagnostic is a sensitive tool for detecting occult breast cancer foci. Due to its limited specificity and high cost, MRI is not likely to become a screening tool for average-risk women. However, the role of breast MRI screening for detecting breast cancer in very high risk women, such as carriers of a BRCA
gene mutation, has now been well established. More controversial are guidelines from the ACS, which recommend that a screening breast MRI be performed in women having at least a 20% lifetime risk for breast cancer, including women having a history of radiotherapy when they were 10 to 30 years of age; or harboring a mutation of \textit{BRCA1}, \textit{BRCA2}, \textit{TP53} or \textit{PTEN}; or having a first-degree relative who harbors one of these mutations.

Several major studies have demonstrated the increased sensitivity of MRI for detecting cancers in women with inherited susceptibility to breast cancer compared with clinical breast examination, mammography, or ultrasonography. The sensitivity of breast MRI is > 75%; in contrast, the sensitivities of mammography and ultrasonography both are < 40%. The combined sensitivity of MRI plus mammography is about 95%, suggesting that it may be a viable strategy for screening young women at high risk for breast cancer.

\textbf{Evaluation of a cystic mass}

\textit{FNA}

When a dominant breast mass is present and the history and physical examination suggest that it is a cyst, the mass can simply be aspirated with a fine needle. Aspiration of a simple benign breast cyst should yield nonbloody fluid and result in complete resolution of the lesion.

\textit{Ultrasonography}

Ultrasound examination can also be used to determine whether a mass is solid or cystic and whether a cyst is simple, complicated, or complex. Simple cysts are anechoic and oval, with thin walls; if asymptomatic, a simple cyst may be treated as an incidental finding. Complicated cysts are similar, except that low-level echoes are present in the cyst lumen. In many instances, complicated cysts may be managed conservatively, unless a worrisome feature or history prompts aspiration. To evaluate complex masses (ie, previously turned complex cysts) that demonstrate a mixed cystic and solid lesion and that occasionally have thickened walls or septa, a biopsy (positive predictive value, 25%) is typically necessary.

\textit{Biopsy}

A biopsy should be considered in the setting of an aspiration that is bloody or for a persistent solid component. Cytologic examination of the fluid is not routinely indicated, as the yield for positive cytology is so low. Cystic carcinoma accounts for < 1% of all breast cancers. However, an intraluminal solid mass is a worrisome sign suggesting (intra) cystic carcinoma and should be biopsied.

\textbf{Evaluation of a solid mass}

A solid, palpable mass can be evaluated in a variety of ways. The decision to observe a patient with a solid breast mass that appears to be benign should be made only after careful clinical and radiologic examinations. Either FNA for cytology or percutaneous core biopsy should also be performed.

\textit{Mammography}

A mammogram is used to assess the radiologic characteristics of the mass and is important for the evaluation of the remainder of the ipsilateral breast as well as the contralateral breast.

\textit{FNA}

This technique is a simple, easy-to-perform method for obtaining material for cytologic examination. The overall incidence of false-positive results ranges from 0% to 2.5% (0.7% when performed by experienced technicians), and the incidence of false-negative results varies from 3% to 27% (3% to 9% in experienced hands). Reasons for false-negative readings include less-than-optimal technique in
preparing the cytologic material, a missed lesion on aspiration, tumor necrosis, and incorrect cytologic interpretation. FNA is limited in its ability to distinguish invasive from noninvasive cancers. For these reasons, the trend at leading breast centers has been to replace FNA with core biopsy.

**Biopsy**

In the past, an excisional biopsy of a small breast mass or an incisional biopsy of a larger breast mass was performed to establish a histologic diagnosis of breast cancer. Recently, excisional biopsies for diagnosis have been largely replaced by percutaneous procedures. For a suspected malignancy, core biopsy has become the preferred diagnostic tool. With a core biopsy, the surgeon can plan for the cancer surgery, allowing for definitive surgical management in a single procedure. Core biopsy is also more advantageous than an FNA because it allows evaluation of architectural and cellular characteristics.

**Image-guided core biopsy**

Ultrasound-guided core biopsies have been shown to offer increased targeting accuracy when compared with freehand core biopsy sampling. In certain limited clinical scenarios, use of vacuum-assisted, large-core needles may help reduce sampling error.

**Evaluation of nonpalpable mammographic abnormalities**

**Excisional biopsy**

Prior to 1991, almost all nonpalpable mammographic lesions were excised using surgical excision. This technique has become less prevalent with the availability of image-guided percutaneous biopsy techniques.

**Stereotactic and ultrasonography-guided core biopsies**

These methods have revolutionized the management of nonpalpable breast lesions, and, currently, the majority of biopsies can be performed percutaneously, which is quicker, less invasive, and less expensive than is excisional biopsy. Tissue acquisition is performed with automated core needles or directional vacuum-assisted biopsy probes. Guidance for percutaneous biopsy is usually provided by stereotaxis, ultrasonography, and, more recently, MRI.

Numerous studies comparing the sensitivity and specificity of stereotactic biopsy versus surgical biopsy have consistently found the two procedures to be statistically equivalent. The long-term false-negative rate for stereotactic biopsy is 1.4%, which equals best published results with surgical biopsy.

Up to 80% of patients with nonpalpable mammographic lesions are candidates for stereotactic core biopsy. Lesions near the chest wall or immediately behind the nipple often cannot be reached on the stereotactic table. Diffuse lesions, such as scattered calcifications or a large asymmetric density, are subject to undersampling with the percutaneous approaches. Some patients are unable to lie prone on the stereotactic table for the duration of the examination. Finally, stereotactic units and trained personnel are not universally available.

Ultrasonography-guided core biopsy is another accurate percutaneous technique, useful for lesions best imaged by ultrasonography. Since the biopsy gun is handheld and guided in real time by the ultrasound imager, its use is related to more variability in performance, depending on the experience and skill of the practitioner. The overall reported accuracy rate of ultrasonography-guided biopsy is comparable with rates achieved with stereotactic and surgical biopsies.

**Ultrasonography-guided or stereotactic FNA**

This biopsy option is somewhat less invasive than core biopsy, but FNA provides only cytologic (not
histologic) pathology results. This technique can result in both false-positive and false-negative results, whereas a false-positive result has not been reported to date for core breast biopsies. FNA is most successful in centers that have an experienced cytopathologist, who, ideally, is available on-site to review smears for adequacy during FNA procedures.

**Breast MRI**

This modality is currently used to search for an occult primary tumor in the setting of known metastasis, evaluate the extent of disease in a biopsy-proven breast carcinoma (useful if breast conservation is being considered), and assess lesions in implant-augmented breasts. It is also useful for screening high-risk women, as described previously. Its role in screening women with dense breasts or for evaluating borderline lesions has not been established, and these indications typically are not reimbursable. Breast MRI has a high sensitivity, and clinical developments have improved its specificity. Breast MRI examinations have recently been facilitated by the development of computer-aided detection software, which can help to streamline the interpretation of these images and produce a more uniform result.

Breast surgeons are increasingly using breast MRI for surgical planning. In a study reported by Bedrosian et al (a retrospective review of 267 patients who had preoperative MRI prior to undergoing definitive surgery), preoperative breast MRI changed the planned surgical approach in 26% of cases, including 16.5% of cases of breast conservation switched to mastectomy. Imaging centers across the United States have a varying degree of expertise in performing, interpreting, and providing a standard reporting nomenclature for breast MRI. The ACR is currently developing an accreditation program in breast MRI to address this issue.

**Ultrasonography**

In investigating ultrasonographic features of solid masses that suggest benign or malignant disease, Stavros et al described such factors as sharp margins (benign) and taller-than-wide lesions (malignant). Although these features are useful for clinical decision-making, their utility in increasing the specificity of the breast lesion workup has not been verified.

**Molecular breast imaging**

Molecular breast imaging has demonstrated excellent specificity and sensitivity in new industry-sponsored trials using high-definition, breast-specific gamma cameras. Both technetium-based sestamibi scanning and breast-specific PET scanning have shown promise. However, their utility has not yet been demonstrated in large-scale clinical trials.

**Prevention**

**Lifestyle changes**

There is increasing evidence that lifestyle changes may alter an individual's breast cancer risk.

**Physical activity**

Exercise has been associated with a reduction in breast cancer risk. The benefit was greatest in younger, premenopausal women. The activity can be related to leisure or work-time activities.

Women who exercise 3.5 to 4.0 times per week may have a reduced incidence of breast cancer, when compared with women who do not exercise. The protective effect of exercise may be associated with a reduction in the frequency of ovulatory cycles and in circulating estrogen and progesterone levels.
**Alcohol consumption**
Numerous studies of the effects of alcohol consumption on breast cancer risk and the results of a cohort study addressing this issue have been published. When compared with nondrinkers, women who consumed 2.3 to 4.5 bottles of beer per day, 2.5 to 5.6 glasses of wine per day, or 2 to 4 shots of liquor per day had a 41% higher risk of developing invasive breast cancer. Some reports indicate that the consumption of a moderate amount of alcohol (red wine) may decrease the risk of breast cancer, although these results are not conclusive. The biologic basis for the association between alcohol consumption and an increased risk of breast cancer is unclear. It has been proposed that there is a positive correlation between alcohol and estrogen levels.

**Alterations in diet and tobacco use**
A reduced incidence of breast cancer has been observed in countries where the diet is typically low in fat. However, no reduction in breast cancer risk has been observed in the United States when women followed low-fat diets.

Prentice et al randomly assigned postmenopausal women without prior breast cancer to an intervention designed to reduce total daily fat consumption to a minimum of 20% or to no dietary intervention. They found no statistically significant reduction in invasive breast cancer risk over a period of approximately 8 years of follow-up. However, women consuming a high-fat diet at baseline showed a significant reduction in breast cancer risk ($P = .04$). The authors also noted an effect that varied by hormone receptor status of the tumor.

There appears to be an association between cigarette smoking and breast cancer risk. It is not clear whether the risk for breast cancer decreases when someone stops smoking.

**Lactation**
Although it has been suggested that lactation may protect against breast cancer, it is unclear whether lactation reduces breast cancer risk. A recent study failed to demonstrate any breast cancer risk reduction in women who breast-fed and showed no dose-response effect in women who breast-fed for longer periods.

**Chemoprevention**
The NIH and NCI have publicized the results of the NSABP BCPT. Women who had a risk of developing breast cancer equivalent to that of women 60 years of age qualified as participants in this double-blind, randomized trial. (For representative eligibility profiles, see Table 5.) A total of 13,388 women were randomized to receive tamoxifen or placebo.

**TABLE 5**
Examples of eligible risk profiles used in the Breast Cancer Prevention Trial

**TABLE 6**
Number of events among participants in the NSABP Breast Cancer Prevention Trial
Benefits of therapy The summary results indicated that tamoxifen prevented about half of both invasive and noninvasive breast cancers in all age groups. A secondary benefit of tamoxifen appeared to be a reduction in the incidence of hip fracture (Table 6). At present, no survival advantage has been shown for participants in this trial.

Side effects Tamoxifen-treated women younger than age 50 had no apparent increase in side effects. However, women older than age 50 experienced serious side effects, including vascular events and endometrial cancer. Particularly worrisome was the increased incidence of endometrial cancer in the tamoxifen-treated patients (Table 6). In addition, a significant increase in pulmonary embolism and deep vein thrombosis was noted, especially in women older than age 50 (Table 6).

Current recommendations Based on results of the BCPT, the FDA has approved tamoxifen for use in women at high risk (1.66% chance of getting breast cancer in the next 5 years, based on the Gail model) of breast cancer.

The NCI and NSABP are in the process of developing risk profiles based on age, number of affected first-degree relatives with breast cancer, number of prior breast biopsies, presence or absence of atypical hyperplasia or LCIS, age at menarche, and age at first live birth. These risk profiles may help guide women in making the decision as to whether or not to take tamoxifen.

An ASCO working group published an assessment of tamoxifen use in the setting of breast cancer risk reduction. All women older than 35 years of age with a Gail model risk of > 1.66% (or the risk equivalent to that of women 60 years of age) should be considered candidates for this treatment strategy. Comorbid conditions, such as a history of deep vein thrombosis, must be a part of the consent process and treatment decision.

Although the BCPT results establish tamoxifen as the standard of care for the primary chemoprevention of breast cancer in high-risk women, concern over the side effects of tamoxifen has prompted a continuing search for an agent that displays a more desirable efficacy/toxicity profile. Raloxifene (Evista), approved for the prevention of osteoporosis in postmenopausal women, and for the reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis, displays antiestrogenic properties in the breast and endometrium and estrogenic effects in the bone, making it an attractive candidate for comparison with tamoxifen.

The CORE trial, a 4-year follow-up to the MORE trial that examined the effect of long-term therapy with raloxifene in postmenopausal women with breast cancer, found that daily intake of the agent reduced the risk of invasive breast cancer by 59%. Compared with placebo, the incidence of invasive estrogen receptor-positive breast cancer was also reduced in the raloxifene arm (P < .001). There was no statistically significant increased risk of blood clots in legs or lungs, between the raloxifene-treated and placebo groups. Long-term use of raloxifene did not increase the risk of uterine cancer, as does long-term use of tamoxifen.

The STAR trial (or NSABP P-2) began in July 1999 at almost 400 centers in North America. A total of 19,747 postmenopausal women, or women > 35 years old at increased risk of breast cancer by Gail criteria, were randomized to receive either tamoxifen (20 mg/d) or raloxifene (60 mg/d) for 5 years. Study endpoints included invasive and noninvasive breast cancers, cardiovascular disease, endometrial cancer, bone fractures, and vascular events.

Vitamin D is a regulator of cellular growth and differentiation. In a prospective Canadian study, vitamin D levels in women newly diagnosed with breast cancer (T1-3, N0-1, M0) more than 10 years before the study began were assessed in archived blood samples taken after surgery and prior to
systemic therapy \((n = 512)\). Vitamin D deficiency was associated with an increased risk of distant recurrence (independent of age, BMI, insulin level, and T and N stage, and not significantly modified by ER status, or use of adjuvant chemotherapy or tamoxifen) and death, while patients with insufficient and sufficient vitamin D levels had similar outcomes. These early findings raise the question of whether vitamin D supplementation might improve breast cancer-specific survival \((Goodwin PJ et al: J Clin Oncol 26[15S]:511, 2008)\).

There were 163 cases of invasive breast cancer in women assigned to tamoxifen and 168 of those assigned to raloxifene (incidence, 4.30 per 1,000 vs 4.41 per 1,000; risk ratio RR, 1.02; 95%, 0.82-1.28). There were fewer cases of noninvasive breast cancer in the tamoxifen group (57 cases) than in the raloxifene group (80 cases); (incidence, 1.51 vs 2.11 per 1,000; RR, 1.40; 95% CI, 0.98-2.00). There were 36 cases of uterine cancer with tamoxifen and 23 with raloxifene (RR, 0.62; 95% CI, 0.35-1.08). The risk of other cancers, fractures, ischemic heart disease, and stroke is similar for both drugs. There was no difference in the total number of deaths (101 for tamoxifen vs 96 for raloxifene) or in causes of death. The authors concluded that raloxifene is as effective as tamoxifen in reducing the risk of invasive breast cancer and has a lower risk of thromboembolic events and cataracts but a nonstatistically significant higher risk of noninvasive breast cancer.

**Staging and prognosis**

![TNM staging system for breast cancer](image)

**TABLE 7**

| TNM staging system for breast cancer |

**Staging system**

The most widely used system to stage breast cancer is the AJCC classification, which is based on tumor size, the status of regional lymph nodes, and the presence of distant metastasis \((Table 7)\).

**Clinical staging**

Assessment of clinical stage is performed initially and is determined after the physical examination and appropriate radiologic studies have been performed.

**Pathologic staging**

Pathologic stage is determined following surgery for operable breast cancer. Pathologic tumor size may differ from clinical tumor size. In addition, axillary nodal metastases that were not clinically evident may be detected after pathologic examination. With the advent of powerful molecular techniques,
isolated tumor cells (ITCs) can be identified in histologically negative nodes. In the current AJCC staging, pathologic staging of nodes for detection of ITCs was included to obtain more information and, it is hoped, gain insight into the biologic significance of these ITCs.

**Prognostic factors**
Numerous prognostic factors for breast cancer have been identified.

**Lymph node status**
Axillary nodal metastasis is the most important prognostic factor in patients with breast cancer. Survival was examined relative to the number of nodes involved and the location of nodes that contained metastatic deposits. For any given number of positive nodes, survival was independent of the level of involvement but was directly related to the number of involved nodes.

Overall, patients who have node-negative disease have a 10-year survival rate of 70% and a 5-year recurrence rate of 19%. As the number of positive nodes increases, so does the likelihood of relapse. Patients with > 10 positive lymph nodes have a recurrence rate of 72% to 82%. The majority of patients who develop recurrence after initial curative treatment of early-stage breast cancer will have distant metastases.

**Hormone-receptor status**
In general, hormone receptor-positive tumors have a more indolent course than do hormone receptor-negative tumors.

**Other factors**
Other considerations used to predict outcome are tumor size, histologic grade, lymphovascular permeation, S-phase fraction, and ploidy. Well differentiated breast cancers have a better prognosis than moderately or poorly differentiated cancers. Likewise smaller tumors are more favorable than larger ones and the absence of lymphovascular invasion is better than its presence.

More recently, molecular prognostic factors have been evaluated to determine their utility in predicting outcome. They include the growth factor receptors (epidermal growth factor receptor and human epidermal growth factor receptor type 2 [HER2]), tumor suppressor genes (TP53), proteolytic enzymes that may be associated with invasion of disease and metastasis (cathepsin D), and metastasis suppressor genes (NME1). Of these molecular markers, HER2 is probably the most widely studied in breast cancer to date.

All breast cancers should be evaluated by immunohistochemistry (IHC) staining for estrogen and progesterone receptor status and HER2 overexpression. The presence of the estrogen (ER) and/or the progesterone receptor (PR) imparts a more favorable prognosis. In addition, these receptors are predictive of response to hormonal therapy. A HER-2 IHC score of 0-1+ is considered negative, 2+ is equivocal, and 3+ is positive. Equivocal HER2-positive tumors undergo fluorescence in situ hybridization (FISH) analysis for evaluation of HER2 gene amplification. HER2 amplification of 2.0 or greater is considered positive. HER2 is also referred to as HER2/neu or ErbB2. It is a 185-kd transmembrane tyrosine kinase that regulates cell growth, survival, migration, differentiation, and adhesion. Overexpression of HER2 leads to dimerization of the receptors, which causes activation of the tyrosine kinase. HER2 overexpression is seen in approximately 20 to 30% of all breast cancers and was traditionally considered a more aggressive and a less favorable disease with reduced disease-free and overall survival. However, the development of biologic agents such as trastuzumab (Herceptin) has revolutionized the treatment of this type of breast cancer.
SUGGESTED READING

On risk factors and genetic cancer risk assessment


on Screening and diagnosis


ON PREVENTION


**Abbreviations in this chapter**

ACR = American College of Radiology; ACRIN = ACR Imaging Network; ACS = American Cancer Society; AMA = American Medical Association; AJCC = American Joint Committee on Cancer; ASCO = American Society of Clinical Oncology; BCLC = Breast Cancer Linkage Consortium; BCPT = Breast Cancer Prevention Trial; CORE = Continuing Outcomes Relevant to Evista; FDA = US Food and Drug Administration; MORE = Multiple Outcomes of Raloxifene; MSKCC = Memorial Sloan-Kettering Cancer Center; NCCN = National Comprehensive Cancer Network; NCI = National Cancer Institute; NIH = National Institutes of Health; NSABP = National Surgical Adjuvant Breast and Bowel Project; STAR = Study of Tamoxifen and Raloxifene; USPSTF = US Preventive Services Task Force; WHI = Women's Health Initiative