A Multidisciplinary Approach to the Management of Breast Cancer, Part 1: Prevention and Diagnosis

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Breast cancer is the most common cancer among women in the United States, with an estimated 200,000 new cases diagnosed annually. A multidisciplinary focus that entails prevention, diagnosis, and treatment has led to significant strides in the reduction of breast cancer incidence and mortality. Additionally, breast cancer management has become increasingly complex, requiring comprehensive assessment and review of multiple issues that include the role of genetic testing, imaging and breast magnetic resonance imaging, surgical and reconstructive options, and a variety of new adjuvant therapies. It has become more evident that a multidisciplinary team approach that involves a spectrum of breast experts is necessary to provide optimal care to patients. This team includes medical oncologists, radiation oncologists, breast pathologists, surgical breast specialists, radiation oncologists, geneticists, and primary care physicians. Furthermore, patient knowledge has increased use of the Internet, and more patients are seeking a multidisciplinary approach to treatment. This review considers information for health care professionals who will facilitate optimal patient care for women at increased risk for or presenting with a new diagnosis of breast cancer. The multidisciplinary team of authors, representing the different disciplines, has selected important state-of-the-art issues that arise in their daily practices for consideration, rather than summarizing what is already available in textbooks.

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Breast cancer is a common disease in women. Approximately one third of cancers in women arise in the breast, making it by far the most commonly diagnosed cancer when basal and squamous cell skin cancers are excluded. In the United States, the American Cancer Society estimates that 180,510 cases of invasive breast cancer and 62,030 cases of breast carcinoma in situ will be diagnosed in 2007, resulting in a woman receiving a diagnosis of breast cancer approximately every 2 minutes. In addition to breast cancer being a diagnostic reality for many women, it is a concern for all women. This emphasizes the importance of knowledge of the disease for all health care professionals who are responsible for the care of women. As more attention has shifted to both primary and secondary prevention of breast cancer, patients are seeking education and information from their primary care physicians about breast cancer risk and options for risk reduction. Primary care physicians who care for women have an important role in addressing breast cancer prevention. With the advent of improved efforts at prevention, screening, and adjuvant therapies, breast cancer mortality has declined.

Prevention

Risk of Developing Breast Cancer

Breast cancer is a complex disease, resulting from the interaction of multiple environmental, hormonal, and lifestyle risk factors with the individual’s genome. Although inherited risk factors are not modifiable, most lifestyle factors are modifiable and are opportunities for breast cancer risk reduction for many women. Application of breast cancer risk prediction models in clinical practice and their role in defining who is at high risk is paramount in targeting management options to match the individual’s underlying risk. Management options for high-risk women include chemoprevention, risk-reducing surgical interventions, and clinical trials. Newer modalities to prevent breast cancer are on the horizon, and clinical trials that evaluate these modalities are promising in their ability to positively impact breast cancer incidence and mortality.

The role of endogenous and exogenous exposure to estrogens in the induction and promotion of breast carcino-
genesis has become an increasingly important risk factor for breast cancer. The mechanism of carcinogenesis is believed to be the result of estrogen stimulation of tissue growth and potentially serum estrogen’s metabolism to genotoxic metabolites.\(^3\)

The cumulative exposure to endogenous estrogen can be associated with reproductive factors, such as early menarche and late menopause. In the postmenopausal state, ongoing estrogen synthesis is secondary to the conversion of androgens (androstenedione and testosterone) via aromatase activity in breast and peripheral adipose tissue. Postmenopausal obesity has been shown to increase breast cancer risk by 50%, and this risk factor is thought to contribute to carcinogenesis on the basis of the presence of increased serum estrone and estradiol concentrations in these patients.\(^4\) Conversely, weight loss or maintenance of ideal body weight (body mass index, 19-25 kg/m\(^2\) [calculated as weight in kilograms divided by the square of height in meters]) and moderate physical activity have been clearly shown to reduce the risk of breast cancer in adult women by approximately 30%.\(^5,6\) Two prospective placebo-controlled trials were conducted by the Women’s Health Initiative in which either estrogen alone (conjugated equine estrogen) or estrogen and medroxyprogesterone were administered and compared with placebo in women with and without an intact uterus, respectively. Although administration of estrogen and medroxyprogesterone increased the incidence of invasive breast cancer by 26% or an excess of 8 cases per 10,000 women-years of follow-up in the women receiving the hormonal therapy and increased the risk of thromboembolism, stroke (41%), and cardiovascular events (29%).\(^7\) Administration of estrogen alone was associated with a trend toward a decreased incidence of breast cancer (hazard ratio [HR], 0.80; \(P=0.09\)).\(^8\)

Findings of epidemiological studies that evaluated oral contraceptives have evolved as a result of changes in hormonal formulations and doses. Although older formulations of oral contraceptives, which contained higher dosages of estrogen and progestins, appeared to increase the risk of breast cancer (among women who used these drugs before 1975),\(^9\) more recent studies have shown that current and former oral contraceptive use is not associated with a significantly increased risk of breast cancer.\(^10\) Similarly, a study of \(BRCA1\) carriers who first took oral contraceptives before 1975, who took them before the age of 30 years, or who took them for 5 or more years may have an increased risk of breast cancer. Although data on \(BRCA2\) carriers were limited, oral contraceptive use did not appear to be associated with risk of breast cancer.\(^11\)

Overall, these studies suggest that estrogen alone is not sufficient for carcinogenesis, and they point to the importance of progestin as an important environmental exposure that increases risk. Increasing knowledge of the role of genetically inherited variation in the pathways that convert estrogen into genotoxic metabolites and pathways involved in conjugation of estrogens may clarify the role of estrogen in breast carcinogenesis.

Age and sex are the most significant nonhormonal risk factors. One in 8 women will develop breast cancer during an expected lifetime of 80 years.\(^12\) A personal history of prior breast biopsies, specifically the finding of atypical hyperplasia, is associated with a 4-fold increase in the risk of breast cancer during a 15-year period.\(^13\) Lobular neoplasia defines a spectrum of histologic changes from atypical lobular hyperplasia to lobular carcinoma in situ (LCIS) that carries a 4-fold to 10-fold increased risk of breast cancer.\(^14\) Women with a strong family history of breast cancer or family members with a known or suspected genetic predisposition to breast cancer are at significant risk for developing this disease. Although only 5% to 10% of breast cancers are associated with a hereditary pattern for these women, the lifetime risk of developing breast cancer in these women is 40% to 80%. Another 15% to 20% of breast cancers have a familial pattern but without a readily identifiable inheritance mechanism. As with any cancer, breast carcinogenesis results from a complex combination of environmental factors that interact with the host genome and influence the body’s response to DNA and cellular damage.\(^15\) Radiation exposure is a classic example, wherein women with Hodgkin lymphoma previously treated with thoracic radiation have a significantly higher risk of breast cancer.\(^16\) Although breast density as noted on mammography carries a 4- to 6-fold increase in breast cancer risk, the underlying genetic factors that confer this risk are unknown.\(^17\)

Modifiable risk factors associated with lifestyle may include alcohol consumption and dietary fat intake. Although multiple cohort studies have reported that consumption of 1 or more alcoholic drinks per day results in an increased risk of breast cancer by approximately 26%,\(^18,19\) no prospective trials have been performed to determine whether the omission of alcohol reduces risk. More recently a study of a low-fat diet among postmenopausal women did not result in a statistically significant reduction in invasive breast cancer risk.\(^6\) Although a low-fat diet during later years did not reduce the risk of breast cancer, such a diet initiated earlier in life may play a role in preventing breast cancer.

**Defining Breast Cancer Risk**

Targeting preventable management interventions is based for the most part on the degree of risk. Breast cancer risk can be categorized as low to average, high, and very high. Women at low to average risk have risk factors that confer
no greater than a 1.5-fold relative risk of developing breast cancer. Elevated or high risk includes women with a Gail model 5-year risk score of 1.66% or higher (defined subsequently), prior history of atypical hyperplasia, or family history that includes 1 affected first-degree relative. Very high-risk women include $BRCA1$ or $BRCA2$ gene mutation carriers and those with a history of LCIS, ductal carcinoma in situ (DCIS), or irradiation before the age of 20 years.

**Breast Cancer Risk Assessment.** To properly assess a woman’s risk of breast cancer, clinicians must take an accurate history, use validated tools to assess the individual’s risk of breast cancer, and understand when to apply risk management strategies based on the degree of risk. The informed decision-making process requires open dialogue and may occur during multiple visits. This process is not urgent but is complicated by a spectrum of options; it is a time-intensive and ongoing process that requires periodic risk reassessment during a woman’s lifetime. Decision aids provide graphical information about breast cancer risk, but the results need to be interpreted in the context of the individual's overall health, beliefs, attitudes, and personality characteristics and factor in the average risk of the population.

**Risk Prediction Models.** The 2 most common breast cancer risk prediction models are the Gail model and Claus model. These models are used to estimate risk and are not absolute indicators of who will develop breast cancer. In contrast, likelihood models are used to predict the probability of $BRCA1$ or $BRCA2$ gene mutation in a given patient or family. These likelihood models take into account a more extensive family history and include both ovarian and breast cancer; examples include the Myriad model, Couch model, and BRCAPRO model. All risk assessment models have strengths and limitations, and no model is comprehensive enough to stand alone as predictive of breast cancer risk. The clinical scenario dictates how to interpret the information and risk estimates. Furthermore, communication and understanding of the perceived risk vs the actual risk are important as part of the decision-making process.

The Breast Cancer Detection Demonstration Project led by Gail et al. was instrumental in defining significant and validated predictors of lifetime risk of breast cancer risk. The National Cancer Institute modified this into a computerized risk assessment tool that calculates the 5-year and lifetime risk of breast cancer as a percentage. A Gail model score of 1.66% or higher is considered high risk and takes into account the following factors: age (model valid only for women >35 years), age at menarche, number of breast biopsies and history of atypical hyperplasia, number of first-degree relatives with breast cancer (mother, sister, or daughter), age at first live birth, and race. The Gail model is available online at www.bcra.nci.nih.gov/brc/ and can be used by the clinician during the office visit. This model does well in predicting the absolute risk of developing breast cancer for women as a group and stratified by various risk factors but does not address the issue of individual risk prediction. This model has other limitations; for example, it is not appropriate for women with a history of breast cancer, LCIS, or DCIS or women who do not undergo annual screening mammography. Also, this model can result in an underestimation of risk in those with an extensive family history of breast cancer, and it does not take into account the paternal side or age of onset of affected relatives. Although the Gail model has limitations and research is needed to identify models with better discriminatory power, it is the model currently approved for use to determine eligibility for tamoxifen therapy for breast cancer risk reduction.

The Claus model is another risk prediction model that incorporates a more extensive family history (first- and second-degree relatives, maternal or paternal, affected by breast cancer and age of affected individuals). The model predicts a women’s absolute risk of developing breast cancer in 10-year increments (between 29 and 77 years of age), culminating in a lifetime risk.

The 3 likelihood models were developed for use by genetic counselors for evaluating women with a strong family history of breast cancer, and each has strengths and limitations. Genetic counselors use these models to determine the probability of an individual patient carrying a genetic mutation. Features of a family history suggestive of a predisposition to hereditary breast cancer include known $BRCA1$ or $BRCA2$ mutation, breast or ovarian cancer within a family of Ashkenazi Jewish ancestry, relatives with bilateral breast cancer, multiple relatives with onset of breast or ovarian cancer at a young age, and male relatives with breast cancer.

Clinicians are advised to refer at-risk women or those with pertinent familial patterns to an established breast clinic or program for risk assessment, counseling, and education. Genetic consultation is a critical component of the evaluation that facilitates discussion regarding risks, benefits, and limitations before proceeding directly to genetic testing.

**Molecular Epidemiology**

The field of epidemiology has traditionally evaluated whether lifestyle factors (e.g., fat intake) are associated with cancer risk. However, with an increased understanding of the molecular processes that underlie carcinogenesis in the context of the mapping of the human genome, the field of molecular epidemiology has emerged. In this discipline, researchers study whether inherited variation in genes that regulate cellular homeostasis affects cancer risk and identify new molecular markers of exposure to make connec-
tions between lifestyle and cancer risk. The ultimate goal of molecular epidemiology is to personalize risk assessment, allowing a more precise estimate of which patients are at higher risk of development of breast cancer. In these patients, more intensive screening, chemoprevention, or prophylactic surgery may ultimately reduce morbidity and mortality associated with breast cancer.

The intraductal approach is a new area of investigation assessing the microenvironment of the breast and tumor biology of breast cancer. This approach encompasses modalities such as nipple fluid aspiration to provide physiologic fluid that can be assessed for novel proteomics, estrogen metabolites, DNA adducts, and other biochemical assays to help identify newer biomarkers. The development of biomarkers may help facilitate more accurate short-term risk assessment and predict response to prevention treatment.

**Risk-Reducing Strategies**

A variety of primary and secondary preventive strategies are available to clinicians who care for high-risk women. Secondary preventive strategies include the combination of clinical breast examinations and breast imaging modalities to detect disease at an earlier stage of progression. Primary preventive strategies include lifestyle modification, chemoprevention, and risk-reducing surgery.

**Surveillance.** The American Cancer Society guidelines for early detection of breast cancer in average risk, asymptomatic women include the following: clinical breast examination as part of the periodic health examination for women in their 20s and 30s to continue annually beginning at the age of 40 years, annual mammography beginning at the age of 40 years, and awareness of new breast symptoms and prompt reporting of changes to their primary care physician. Enhanced surveillance is important in women at high or very high risk and includes having a clinical breast examination performed every 6 to 12 months and annual mammography. In these women, the age at which to initiate mammography should begin 5 to 10 years earlier than the youngest affected relative or at the age of 40 years, whichever is earlier. Studies that assess contrast-enhanced breast magnetic resonance imaging (MRI) as a screening tool for very high-risk women report a very high sensitivity for detecting invasive breast cancer. However, given that the specificity ranges from 37% to 97%, the risks, benefits, and limitations of this study must be thoroughly discussed.

The American Cancer Society recently issued guidelines, after review of the evidence, for breast screening with MRI as an adjunct to mammography for specific levels of risk. On the basis of this review, screening MRI is recommended for women with a strong family history of breast and ovarian cancer, carriers of the *BRCA* mutation, women with a history of chest radiation between the ages of 10 and 30 years for Hodgkin disease, and women with a lifetime risk greater than 20% to 25% as defined by risk prediction models dependent on family history. Risk groups for which evidence is insufficient to recommend for or against screening include women with a personal history of invasive or in situ breast cancer, atypical hyperplasia, and extremely dense breasts on mammography.

**Risk-Reducing Surgery.** Risk-reducing mastectomy, although considered an aggressive option, is a reasonable and effective option in very high-risk women (hereditary predisposition to carrying a genetic mutation or *BRCA1* or *BRCA2* gene mutation carriers). Hartmann et al first reported that in high-risk women (those with a family history of breast cancer), prophylactic mastectomy reduced the incidence of breast cancer by 90%. In contrast, prophylactic oophorectomy decreases ovarian cancer by at least 95% and breast cancer risk by 50% if performed before the age of 40 years. Prophylactic oophorectomy is more often the initial choice for risk reduction because it is not associated with alteration in body image and self-esteem, as can occur after prophylactic mastectomy. Women who spend the necessary time exploring their options and share information with family members and friends are more accepting of their decision to have risk-reduction surgery in the long term.

**Chemoprevention**

**Tamoxifen.** Tamoxifen, a first-generation selective estrogen receptor modulator (SERM), has both estrogenic and antiestrogenic properties, and its mechanism of action against breast cancer is estrogen receptor blockade. In 1998, the Food and Drug Administration (FDA) approved the use of tamoxifen, 20 mg/d for 5 years, for breast cancer risk reduction in high-risk individuals.

A placebo-controlled trial of tamoxifen as adjuvant therapy showed a reduction in contralateral breast cancer. Subsequently, 4 randomized trials that prospectively evaluated tamoxifen and 1 meta-analysis (involving the National Surgical Adjuvant Breast and Bowel Project [NSABP] P-1, the International Breast Cancer Intervention Study, a Royal Marsden Hospital study, and an Italian study) led to further support of tamoxifen as a risk-reducing drug. The NSABP P-1 trial was the first and largest (N=13,388) of the randomized studies that compared tamoxifen to placebo. Eligibility for this trial included women older than 35 years and those at high risk based on a Gail model 5-year risk score of 1.66% or higher, prior LCIS, or history of atypical ductal or lobular hyperplasia. After 4 1/2 years of treatment with tamoxifen, a 42% reduction in breast cancer occurred (relative risk [RR], 0.58; 95% confidence interval [CI], 0.38-0.84), and the risk reduction benefit was seen across
all age groups. In women with LCIS, a 56% reduction was seen, and in those with atypical hyperplasia, an 86% reduction was seen. Noninvasive breast cancer was reduced by 50%, and estrogen receptor–positive tumors were decreased by 69%. The meta-analysis, including the 4 trials aforementioned, reported a 38% reduction in breast cancer with tamoxifen (odds ratio, 0.62; 95% CI, 0.42-0.89). However, none of the 4 trials showed a mortality benefit with tamoxifen use. Furthermore, women need to be informed of the adverse effects of tamoxifen, which include hot flashes, vaginal discharge, and other significant risks, such as endometrial cancer (2 per 1000 women per year), stroke (2-fold increased risk), and life-threatening thromboembolic disease (2- to 3-fold increased risk). These risks appear to be less pronounced in premenopausal women and increase significantly in postmenopausal women and those with other medical comorbidities.29

Raloxifene. Raloxifene is a second-generation SERM with estrogen antagonist properties similar to tamoxifen but with a less agonistic effect on the endometrium. Raloxifene increases bone mineral density in postmenopausal women and reduces the risk of vertebral fracture; it is approved by the FDA for the prevention and treatment of osteoporosis. The MORE (Multiple Outcomes of Raloxifene Evaluation) trial was a study of postmenopausal women with osteoporosis who were randomized to raloxifene or placebo in which a secondary aim of breast cancer incidence was predefined. This trial (N=7705) found that the incidence of breast cancer was reduced by 72% after 4 years and was the first study, to our knowledge, to show a possible breast cancer risk reduction effect with raloxifene therapy.34

The CORE (Continuing Outcomes Relevant to Evista) trial, completed in 2004, was designed to evaluate the efficacy of an additional 4 years of raloxifene therapy in preventing invasive breast cancer. During the 8 years of both trials, the incidence of estrogen receptor–positive invasive breast cancer was reduced by 66% (HR, 0.34; 95% CI, 0.22-0.50) and 76% (HR, 0.24; 95% CI, 0.83-5.70), respectively. No new safety concerns related to raloxifene therapy were identified during this trial.35

Raloxifene, in these trials, appeared to have a similar side effect profile as tamoxifen in terms of increased risk of thromboembolic disease (2-fold increased risk) and stroke and exacerbation of vasomotor symptoms. However, unlike tamoxifen it does not result in an increased risk of endometrial cancer. With regard to heart disease, the RUTH (Raloxifene Use for The Heart) trial reported no significant reduction in cardiovascular disease among women with multiple cardiac risk factors or prior history of cardiovascular disease. However, an increased risk of fatal stroke and venous thromboembolism was found in this high-risk group.36

An important prevention study was the NSABP P-2 STAR (Study of Tamoxifen and Raloxifene) trial, a prospective, randomized, double-blind study of 19,747 postmenopausal (mean age, 58.5 years) high-risk women (eligibility similar to NSABP P-1). The NSABP investigators found that raloxifene was as effective as tamoxifen in reducing the risk of invasive breast cancer (RR, 1.02; 95% CI, 0.82-1.28). Interestingly, the occurrence of noninvasive breast cancer was lower with tamoxifen (RR, 1.40; 95% CI, 0.98-2.00) although the reason is not entirely clear. Thromboembolic events and cataracts were significantly less among women taking raloxifene compared with tamoxifen. Among women taking raloxifene, fewer cases of uterine hyperplasia occurred, but the uterine cancer risk was similar between both groups. With regard to quality of life and patient-reported outcomes and symptoms, women in the tamoxifen arm reported more vasomotor symptoms, leg cramps, and gynecological problems but better sexual function. Those taking raloxifene reported more dyspareunia, weight gain, and musculoskeletal problems.38 On the basis of the findings from the STAR trial, it appears that raloxifene represents an alternative to tamoxifen in women who want to take a SERM and who are willing to accept the potential adverse effects of this therapy. Raloxifene is not recommended for treatment in premenopausal women.

Aromatase Inhibitors. Aromatization of androgens (androstenedione or testosterone) by the aromatase enzyme in peripheral tissues such as fat and muscle is a major source of estrogens in postmenopausal women. Aromatase inhibitors (AIs) include first-, second-, and third-generation drugs and significantly reduce the amount of estrogen in breast tissue. Third-generation drugs, unlike the first- and second-generation drugs, do not alter cortisol or aldosterone plasma levels. Third-generation drugs include anastrozole and letrozole, which are both nonsteroidal AIs and bind to the P-450 site of the aromatase complex, and exemestane, a steroidal AI that binds to the substrate-binding pocket, resulting in aromatase inactivation. All 3 have comparable degrees of estrogen suppression (96%-99%) and lower estrogen levels in the breast and in other tissues.39

To date no completed randomized clinical trials have evaluated AIs in breast cancer prevention. The 3 AIs have been studied in adjuvant breast therapy trials (compared with tamoxifen) and have consistently shown a benefit in reducing contralateral breast cancer. These studies have led the way for new chemoprevention trials that will define the benefit-risk ratio of these agents.

American Society of Clinical Oncology Technology Assessment: Chemoprevention 2002. This ongoing comprehensive literature review of evidence-based chemopreventive strategies for breast cancer reduction has to date highlighted that placebo controls are appropriate for breast
cancer risk reduction since no intervention has demonstrated a favorable net impact on overall health or survival. The tamoxifen trials have not shown that the drug in the chemoprevention setting provides an overall benefit or increased survival.\(^{40}\)

Women with a defined 5-year projected breast cancer risk score of 1.66% or higher may be offered tamoxifen at 20 mg/d for 5 years to reduce their risk of breast cancer. The risk-benefit models suggest that the greatest clinical benefit with the fewest adverse effects derived from tamoxifen use is observed in younger (premenopausal) women who are less likely to have thromboembolic sequelae and uterine cancer or in women who have had a hysterectomy. Tamoxifen use should be discussed as part of an informed decision-making process with careful consideration of individually calculated risks and benefits.\(^{41}\)

**Ongoing Prevention Trials.** The National Cancer Institute of Canada is conducting a prevention trial comparing exemestane to placebo in a study known as MAP-3 (Mammary Prevention 3) that involves postmenopausal women. The 5-year study has a projected accrual of 4500 women. Eligibility for this trial includes a Gail model 5-year risk score of 1.66% or higher, age 60 years and older, prior atypical ductal or lobular hyperplasia, or DCIS treated with mastectomy alone. This multicenter study includes sites in the United States, Canada, and Spain.\(^{42}\)

The International Breast Cancer Intervention 2 trial began in Europe in February 2003 and is comparing anastrozole to placebo in 6000 postmenopausal women at increased risk of breast cancer with a secondary aim of assessing osteoporosis incidence. This trial has similar high-risk entry criteria as were aforementioned for the MAP-3 trial with the addition of increased mammographic density. A second complementary study will address the role of anastrozole vs placebo in women with DCIS.\(^{42}\)

A third study, the Aromasin Prevention Study, is under way in Italy and is evaluating exemestane vs placebo in \(BRCA1\) and \(BRCA2\) gene mutation carriers during 5 years. The primary aim includes the incidence of breast cancer, and secondary aims involve the incidence of LCIS, DCIS, toxicity, bone mineral density, and quality of life.\(^{42}\)

**DIAGNOSIS**

The multidisciplinary approach to the work-up of newly diagnosed breast cancer includes a team of breast experts, including internal medicine (primary care and nursing), radiology, pathology, surgery, and medical oncology specialists.

**BREAST IMAGING**

Mammography is the most established method for imaging the breast and is the primary tool for breast disease evaluation. Asymptomatic women undergo screening mammography, which entails 2 views of each breast: the craniocaudal view and the medial lateral oblique view. Women with symptoms such as a palpable abnormality, skin changes, or nipple discharge undergo diagnostic mammography, which is also used for further evaluation of abnormal findings on a screening mammogram. Besides the standard 2 views of each breast, diagnostic mammography may include additional mammographic magnification views or spot compression views. Ultrasonography is frequently used as an adjunct to diagnostic mammography. Most women with a palpable abnormality will undergo a focused ultrasonographic examination involving the area of clinical concern. Additionally, ultrasonography is often used to further characterize a mammographic abnormality and is a common guide for breast intervention.

A meta-analysis of randomized trials studying the effectiveness of screening mammography demonstrates reductions of 20% to 35% in mortality due to breast cancer for women aged 50 to 69 years.\(^{43}\) The benefit of screening women in their 40s is slower to appear and is somewhat less than that for women older than 50 years.\(^{44}\) The goal of screening mammography is to detect breast cancer early before it becomes symptomatic and before it spreads to lymph nodes. The American College of Radiology has established that more than 50% of breast cancers diagnosed in a successful mammography practice should be stage 0 or 1 and more than 30% should be invasive cancers that are 1 cm or smaller or DCIS.\(^{45}\) The prevalence of breast cancer found on first-time screening mammograms is between 6 and 10 per 1000 women. The incidence of cancers found on follow-up screening mammography is between 2 and 4 per 1000 women.\(^{45}\)

The widely accepted definition of a false-negative mammogram is a negative mammogram within the year before the breast cancer diagnosis. This number is used to calculate the sensitivity of mammography.\(^{45}\) The overall sensitivity of mammography for breast cancer detection is approximately 85%.\(^{46,47}\) However, studies that evaluate only women with \(BRCA\) mutations and dense breasts report sensitivities of only 38% to 55%.\(^{48,49}\) Breast cancer often has the same density as normal fibroglandular tissue, making detection more difficult in dense breasts. The American College of Radiology Breast Imaging and Reporting Data System divides breast density into 4 categories. A density of 1 represents breasts that are composed of less than 25% dense tissue, whereas a density of 4 signifies that more than 75% of the breast is composed of dense tissue.\(^{45}\) Breast density is a known limitation of mammography and one reason that other methods for screening women with dense breasts are desirable.

Digital mammography may provide improved cancer detection in women with dense breasts. In a recent study,
42,760 women at 33 centers underwent both digital and film mammography. In the population as a whole, the diagnostic accuracy of film and digital mammography was similar. However, digital mammography was significantly more accurate in women with dense breasts. The advantage of digital mammography seems to be the ability to manipulate image contrast during interpretation to enhance the visibility of subtle lesions. Currently, digital mammography is not widely available, and the cost is prohibitive for many breast centers.

In recent years, computer-aided detection (CAD) systems have been approved by the FDA for screening and diagnostic mammography. The CAD systems are designed to serve as a “second reader,” prompting review of marked areas. The interpreting radiologist determines whether action needs to be taken on a CAD marker. A study that evaluated CAD found a 7.6% increase in cancer detection, and 5 of 8 cancers detected only by CAD in that study were DCIS presenting as microcalcifications. The CAD system did not mark 24% of the cancers that were detected by the radiologist.

The utility of whole breast screening ultrasonography is currently being investigated in a large multi-institutional study. Published single-institution studies indicate that the cancer detection rate of screening ultrasonography in women with a negative mammogram and clinical breast examination is 2.7 to 4.6 per 1000 women. Although painless and relatively inexpensive, ultrasonography is highly operator dependent and has a high false-positive rate. In screening studies, the positive predictive value of an ultrasonography-detected lesion that undergoes biopsy is approximately 10% compared with 35% for a mammography-detected lesion.

Breast MRI is another imaging modality that is used as an adjunct to diagnostic mammography. It is also a screening tool in select high-risk women. Similar to ultrasonography, the effectiveness of MRI is not limited by breast density. The sensitivity for invasive cancer is 77% to 100% in published series, and the negative predictive value is very high in problem-solving situations. Preoperative MRI in women with a new diagnosis of breast cancer can assess tumor extent more accurately than mammography and detect additional sites of unsuspected ipsilateral cancer in 6% to 34% of cases. Unsuspected contralateral malignancy, detected only with MRI, is found in 3% to 5% of women with a new diagnosis of breast carcinoma. Specificity is a limitation of breast MRI, primarily because of overlap in the appearance of malignant and benign disease, leading to additional work-ups, biopsies, and anxiety for MRI-detected benign disease. The cost, time, and false-positive result issue make it unlikely that MRI will become a screening tool in the general population. In the high-risk patient, investigators consistently find a higher sensitivity with MRI than mammography. However, the impact on survival has not been demonstrated, and randomized studies have not been performed.

Core needle biopsy with ultrasonography, stereotactic (mammographic), or MRI guidance is routinely performed for diagnosing indeterminate breast lesions. Core needle biopsy with imaging or pathology correlation is very accurate. The positive predictive value for cancer diagnosis with core needle breast biopsy is 25% to 40%. For women with a benign lesion at core biopsy, surgery is unnecessary. For those with cancer, the core biopsy results are useful for therapeutic planning.

**Breast Pathology and Surgical Management**

The pathologist’s primary responsibility is to establish the histologic diagnosis and anatomic extent of the tumor. Determining whether the breast carcinoma is in situ or invasive is an important factor. Pathologists closely examine and report the gross, histologic, and molecular characterization of the breast tumor. This information is then directly used by the treating clinician to estimate prognosis, select adjuvant therapy (eg, chemotherapy and/or hormonal therapy), and estimate benefit of therapy. Accurate reporting of pathological test results is of the utmost importance, and strict guidelines have been set forth by the Cancer Committee of the College of American Pathologists to accomplish this mission.

Screening mammography programs have led to a substantial increase in the detection of DCIS, which accounts for approximately 20% of newly diagnosed breast cancers. The hallmark of DCIS is the neoplastic proliferation of epithelial cells confined to the ductal-lobular system without stromal invasion. In principle, DCIS has no metastatic potential. However, 1% to 2% of patients diagnosed as having DCIS will eventually develop distant metastases. This phenomenon is explained by occult invasion not detected in the original lesion or progression of the residual DCIS lesion to invasive carcinoma. Treatment options available for patients diagnosed as having DCIS include breast-conserving surgery with radiation (with or without adjuvant tamoxifen therapy) or total mastectomy. The consideration for adjuvant radiation and/or hormonal therapies is based on data from multiple randomized controlled trials showing that radiotherapy consistently reduces the risk of local recurrence by approximately 50% and that the addition of tamoxifen to lumpectomy and radiotherapy significantly reduces the incidence of cancer events in estrogen receptor–positive tumors. Prognosis for patients diagnosed as having DCIS is associated with tumor size, nuclear grade, distance to the surgical resection margin, estrogen receptor status, and age, with margin...
status proving to be a significant indicator of local tumor control.76,77

Given the fact that more women are choosing breast-conserving surgery over mastectomy, the question of what constitutes an adequate pathological excision margin still remains. We know that among patients treated with or without radiation therapy, significantly higher local recurrence rates were observed when the surgical resection margins were positive than when the surgical resection margins were negative.78 Therefore, achieving negative margins in patients treated with breast-conserving surgery is clinically important. To evaluate the status of the resection margins, the specimen is inked many times with different-colored inks that designate various margins before sectioning. Numerous studies have been conducted to address the best method (shaved vs perpendicular vs separate cavity sampling) of margin assessment and the ideal distance to the resection margin to obtain good clinical outcome.79,81 No single best accepted method for margin assessment has been identified, and the choice of the method used may depend in part on the clinical circumstance. Moreover, several studies have shown that the local recurrence rate decreases as margin width increases.77,82 For that reason, the question has been raised about whether there is a subset of patients diagnosed as having DCIS who have a low risk of recurrence such that wide excision alone is sufficient treatment. The hypothesis that small low-grade DCIS lesions excised with margins of at least 1.0 cm may not need the addition of radiotherapy has been suggested. Unfortunately, given the current evidence, no such subset of patients has been identified,77,83,84 although a prospective clinical trial of surgery alone has been performed and published results are awaited.

Multiple factors have been proven to be of prognostic importance and useful in the clinical management of patients with invasive carcinoma. Tumor size, presence or absence of lymph nodes, and histological grade are the 3 factors considered to be the gold standards by which novel prognostic factors are judged. The size of the tumor is one of the most powerful predictors of tumor behavior in breast cancer.85,86 Accurate assessment of tumor size is important to stratify patients properly, especially since screening mammography has resulted in a larger number of smaller tumors. The tumor is staged on the basis of the largest dimension of the invasive component. When 2 or more distinct invasive tumors are present, staging is based on the size of the largest tumor; the tumors sizes are not added together to create a single larger measurement.68

The histological grade and histological type of invasive tumor also allow risk stratification within a given tumor stage and thus are important determinants of prognosis.87 The Nottingham combined histological grade (Elston-Ellis modification of the Scarff-Bloom-Richardson grading system) has been validated and is widely accepted.88-90 This grading system is based on 3 morphologic features: tubule formation (glandular differentiation), nuclear pleomorphism, and mitotic activity. The importance of this grading system is endorsed in the 6th edition of the AJCC (American Joint Committee on Cancer) Cancer Staging Manual, and this system is considered mandatory.91 The most common type of invasive carcinoma is ductal or no special type and comprises approximately 60% to 75% of all invasive tumors. The reported frequency of invasive lobular carcinoma varies considerably and ranges from 1% to 15%.92 The remaining histological types are considered special types (eg, tubular carcinoma, mucinous carcinoma), and most are associated with favorable prognosis.

Estrogen receptor and progesterone receptor testing should be performed on all primary invasive carcinomas and intraductal carcinomas based on the recent findings from the NSABP Protocol B-24.94 The presence or absence of estrogen and progesterone receptors determines clinical response to hormonal therapy and thus is used in the routine management of patients with breast cancer.68,95 Immunohistochemical analysis is the current choice for estrogen assessment, and its predictive value has been shown to be superior to that of biochemically based ligand-binding assays.96 New treatment recommendations presented at the ninth St Gallen (Switzerland) consensus conference emphasized the importance of endocrine responsiveness in choosing appropriate adjuvant systemic treatments for the patient with invasive breast carcinoma.97 Therefore, the percentage or proportion of tumor cells that express estrogen and progesterone receptors ideally should be specified in the pathology report.

erb2 (HER2-neu) is overexpressed and/or amplified in 20% to 30% of invasive breast carcinomas.98 The 2 most common commercially available assays use immunohistochemical analysis and fluorescence in situ hybridization (FISH) and have been approved by the FDA. The issue of whether immunohistochemical analysis or FISH is a superior determinant of HER2-neu status remains a topic of debate. The commercial kit for immunohistochemical testing uses a 4-part grading system (0-3+) based on quantitative and staining intensity. Scores of 0 to 1+ are considered negative, whereas scores of 3+ are considered positive. Poor correlation exists between weak positivity (2+) by immunohistochemical analysis and gene amplification by FISH; therefore, an algorithm has been proposed that all tumors with weak positivity by immunohistochemical analysis also be evaluated by FISH before making a decision to recommend anti-HER therapy.99

The most important predictor of disease-free and overall survival in breast cancer has been axillary lymph node
status. A correlation has been found between the number of positive lymph nodes and patient prognosis, with worse prognosis associated with an increased number of positive lymph nodes.

The most important surgical development in breast cancer treatment during the past 10 years has been the adoption of the sentinel lymph node biopsy (SLNB) as the preferred technique for axillary staging in invasive cancer. Before the use of SLNB, axillary dissection was the standard procedure for both axillary staging and regional control in the axillary basin. However, axillary dissection has substantial attendant morbidity, including lymphedema, sensory deficits, chronic pain, motor nerve injury, depression, and reduced quality of life. In most node-negative women with breast cancer, axillary dissection is a morbid technique for proving that the nodal basin is clear of disease, and a less invasive procedure to identify this group is valuable.

The SLNB is based on the concept that metastasis of a primary tumor follows drainage of breast lymphatics to a sentinel lymph node before other lymph nodes in the basin. Therefore, if the sentinel node or nodes are negative, higher echelon nodes are assumed to be negative, and axillary dissection can be avoided. Multiple validation studies that correlate findings of SLNB with concomitant axillary dissection have proven the high accuracy of this procedure, with false-negative rates consistently less than 10% and often less than 5%. In the SLNB procedure, the sentinel nodes are located (mapped) via draining breast lymphatics by injection of tracer agents (radioisotope, blue dye, or both) in the breast preoperatively. At surgery, lymph nodes that are hot, blue, or palpably suspicious for disease are considered sentinel nodes and are removed. Although SLNB can be performed with a single tracer, the American Society of Breast Surgeons recommends the use of both blue dye and isotope for optimal mapping accuracy. As expected, SLNB has proven to be less morbid than axillary dissection. Therefore, in cases in which the sentinel lymph node or nodes are negative for metastasis, no axillary dissection is necessary, reducing surgical morbidity for most node-negative patients. In contrast, for cases with positive sentinel nodes, the SLNB procedure has created some management controversies.

The removal of only a few sentinel lymph nodes allows more careful histologic evaluation of this tissue compared with what has been done with an axillary node excision pathologic specimen. Furthermore, immunohistochemical staining to detect cytokeratin-positive cells has resulted in a subset of patients having isolated tumor cells or very small metastases. The AJCC staging system was modified in 2000 and further stratifies nodal findings for the N1 category based on the measured size of metastasis. For patients with sentinel node metastasis that measures less than 0.2 mm (including those with isolated tumor cells), the tumors are considered node negative and are denoted N0(1+). These patients (a minority of those with sentinel node findings) should be treated as node negative because the clinical importance of these subtle histologic findings is unclear. However, some evidence indicates that these patients are being upstaged, with resulting concerns of overtreatment and its related toxicity.

In cases with a true-positive sentinel node (metastasis >0.2 mm), completion axillary dissection remains the standard of care for both local control and prognostication. Some centers use intraoperative analysis of sentinel nodes (either frozen section or touch preparation cytologic testing) and then proceed immediately to axillary dissection, completing all necessary surgical procedures during 1 operation. However, these intraoperative analyses will still miss some sentinel node metastases found later with permanent sections, leading to the challenging postoperative discussion with the sentinel node–positive patient who has not undergone an axillary dissection. For patients who have already been staged as having node-positive disease, many physicians question the need for axillary dissection since these patients will receive adjuvant systemic treatments and possibly also low axillary radiation as part of standard breast radiation with tangents. A recent randomized trial was designed to address the need for completion axillary dissection in the event of a positive sentinel node (ACOSOG [American College of Surgeons Oncology Group] Z0011), but this trial closed early because of poor accrual and has had fewer events than expected in both treatment arms.

Of patients with a positive sentinel node, approximately 40% to 60% have no other involved nodes and would not be expected to benefit from axillary lymph node dissection. When the sentinel node is the only node with metastasis, sentinel lymphadenectomy is diagnostic and therapeutic. Therefore, some research efforts have focused on creating predictive models to identify patients who will have no disease in the remaining nonsentinel nodes. Early studies noted that nonsentinel node metastasis was much less common in patients with micrometastasis in the sentinel node. A model to estimate the risk of additional nodal metastasis was developed at the Memorial Sloan-Kettering Cancer Center on the basis of common clinicopathologic characteristics. This model has been validated in other patient populations with acceptable, but variable, performance. Although overall model performance for a population may be good, its ability to identify patients without additional nodal disease (based on a low-risk calculation) may not be highly reliable in that same population.

Some node-positive patients have chosen not to undergo a second operation for completion axillary dissection. The
limited published literature in such cases demonstrates a negligible rate of axillary recurrence, with follow-up ranging from 28 to 32 months. Not surprisingly, one study has confirmed that node-positive patients who do not undergo axillary dissection are not a random subset of node-positive patients; they are significantly different than those who undergo axillary dissection based on multiple clinicopathologic characteristics. As one might expect, patients who forgo axillary dissection are older, have smaller tumors, and have a lower burden of metastasis in the sentinel node or nodes. These reports confirm that some patients and clinicians in current practice judge the risk of axillary dissection to be greater than its benefit, and axillary recurrence rates in these patients may be low enough that omission of axillary dissection is a reasonable approach for some sentinel lymph node–positive patients. Although axillary dissection remains the current standard of care for patients with sentinel lymph node–positive breast cancer, this is a controversial issue that deserves further study.

**Staging and Prognostic Indicators**

Because staging systems take into account the extent of tumor spread in the body, they serve as critical guides to physicians in deciding appropriate treatment strategies and in discussing an individual patient’s prognosis as the risk of developing metastasis increases with the presence of lymph node involvement and/or a larger primary tumor. The currently used TNM (representing tumor-node-metastasis) staging system for breast cancer reflects the revisions implemented in 2003 by the AJCC to account for developments in biomarker assays, imaging, and surgical techniques. It maintains the traditional dual approach of pretreatment clinical staging complemented by postsurgical histopathologic examination. (Full details on staging are available at http://nccn.org/professionals/physician_gls/PDF/breast.pdf.) Careful physical examination and history taking are the key elements in clinical staging for breast cancer, particularly since additional imaging studies, such as computed tomography, bone scans, MRI, or positron emission tomography, are sometimes used to investigate abnormal blood test results (eg, elevation of liver enzyme levels, bone fraction of serum alkaline phosphatase) and also to evaluate patients who present with locally advanced disease. When multiple tumors are present in the same breast, only the largest is measured to determine the T stage. Metastatic deposits within axillary fat are considered positive axillary nodes, as are positive intramammary nodes, even though the actual axillary nodes are negative.

Decision making on adjuvant treatment recommendations is a complex process that involves integration of probabilistic estimates of risk of breast cancer recurrence and death due to breast cancer as well as competing health risks with actuarial survival in the context of efficacy data of available treatment. Although the TNM system is well established as a prognostic tool, it does not reflect the biological heterogeneity of breast cancer; thus, it fails to account for approximately one third of women with node-negative breast cancer who eventually develop distant metastases, whereas another one third of patients with nodal involvement of breast cancer remain free of distant metastases 10 years after local therapy. Thus, various prediction models, such as the validated Adjuvant! Online tool (www.adjuvantonline.com), have incorporated multiple other variables (eg, tumor grade) to help individualize risk assessments.

Studies have shown that loss of histopathological differentiation (tumor grade) and presence of lymphovascular invasion are associated with an increased risk of distant recurrence, especially in node-negative breast cancer. The expression of estrogen receptor is generally but not consistently reported to be a favorable prognostic factor. This prognostic significance is posited to be time dependent, arising from treatment effect because of the correlation of better response to tamoxifen in tumors with high estrogen receptor levels. Outcomes among postmenopausal women who did not receive adjuvant endocrine treatment were most favorable for those whose tumors had intermediate expression compared with those whose tumors had high expression of estrogen receptors. Moreover, when treated with chemotherapy alone, premenopausal women younger than 35 years with estrogen receptor–positive tumors seem to have significantly worse disease-free survival rates than younger patients with estrogen receptor–negative tumors.

Amplification or overexpression of HER2/neu has been associated with poor survival outcome in patients with axillary lymph node metastases. Although its prognostic value is deemed weak to moderate, testing for HER2/neu status is routine because it is a predictive marker for response to chemotherapy, endocrine therapy, and agents directed against HER2, such as trastuzumab and lapatinib.

Conversely, the negative prognostic effect on survival outcomes after detection of tumor cell dissemination, either in circulation or in the bone marrow, remains controversial and must be further substantiated by standardized detection and quantification procedures before clinical use becomes widespread.

In recent years, mathematical algorithms based on gene expression profiles have been added to the arsenal of prognostic tools. On the basis of unsupervised clustering analysis, 3 biologically distinct subtypes of estrogen receptor–negative and 2 of estrogen receptor–positive breast cancers were identified that represented clinically distinct subgroups of patients. For example, estrogen receptor–
positive luminal A subtype tumors have the best outcome of all subtypes.\textsuperscript{149,150}

On the basis of a supervised analytical approach, different gene signatures have also been developed to harness the prognostic and predictive power of genome-wide interrogation. A 70-gene signature (MammaPrint) was developed based on a cohort of young patients (<55 years) with lymph node–negative breast cancer to assess 5-year disease recurrence, although estrogen receptor status and other clinical variables were not considered.\textsuperscript{151} The classification based on this gene profile outperformed other risk classification criteria and applied just as well to patients with nodal involvement, implying that acquisition of metastatic potential is an early event in tumorigenesis.\textsuperscript{152} It is the first multigene prognostic test that received FDA approval (in February 2007). Using an alternative microarray platform that accounts for estrogen receptor status, a gene expression signature of 76 genes also outperformed traditional risk criteria in predicting 5-year distant recurrence outcomes in patients of all age groups with lymph node–negative breast cancer, particularly for estrogen receptor–positive subgroups.\textsuperscript{153,154} For patients with node-negative estrogen receptor–positive breast cancers who have been treated with adjuvant tamoxifen, an independently prognostic 21-gene signature profile (OncoType DX) has been developed to generate a recurrence score that quantifies individual risk of distant disease in this group of patients.\textsuperscript{155} Although this information may help patients and physicians decide on the utility of adjuvant systemic chemotherapy depending on the recurrence risk score, this test will be of questionable value in patients not receiving adjuvant systemic therapy.\textsuperscript{156-158} This finding led to the recent opening of a large randomized clinical trial (TAILORx [Trial Assigning IndividuAlized Options for Treatment (Rx)]) in which patients with node-negative, estrogen receptor–positive breast cancer with an intermediate risk prognosis according to OncoType DX are randomized to either hormonal therapy alone or chemotherapy followed by hormonal therapy. The trial is powered to establish nonsuperiority between these 2 treatment arms but only in patients with intermediate-risk tumors. In contrast, there is no randomization in either the high- or low-risk group. Patients with low-risk scores are offered only hormonal therapy, whereas patients with high-risk scores are offered chemotherapy followed by hormonal therapy.

**CONCLUSION**

Breast cancer care requires a multidisciplinary approach. The team of breast experts includes primary care physicians (internists, family medicine specialists, and nurses), geneticists, breast radiologists, breast pathologists, surgical breast specialists, and radiation and medical oncology specialists. The complexity of breast cancer has increased with the advent of risk-reducing strategies, breast imaging technology, new drug therapies, and the integration of genomics into the evaluation and treatment of patients. As each member of the team focuses on his or her area of expertise, patients benefit from the collaboration, and overall this provides optimal, quality patient care.

Part 2 of this contribution will provide a comprehensive overview of new adjuvant therapies. The overview will describe the role of partial breast radiation, adjuvant hormonal and systemic options, tamoxifen pharmacogenetics, and anti–HER2 therapy with the goal of providing caregivers with state-of-the-art treatment for breast cancer.

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