# 2 Primary Prevention of Breast Cancer, Screening for Early Detection of Breast Cancer, and Diagnostic Evaluation of Clinical and Mammographic Breast Abnormalities

*Therese B. Bevers*

## Chapter Overview

Breast cancer prevention recommendations are risk based, so determination of an individual woman's breast cancer risk is a first step in designing a prevention and screening plan. A computerized breast cancer risk assessment tool that calculates an individual woman's risk of breast cancer is available for use in the clinical setting. Once a woman is identified as being at increased risk for breast cancer, she needs to be counseled regarding her options to reduce that risk. While lifestyle modification can be suggested as a healthy maneuver, its benefit in reducing breast cancer risk remains uncertain. Prophylactic surgical strategies (oophorectomy and mastectomy) have been demonstrated to significantly reduce breast cancer risk, but because the physiological and psychological consequences can be significant, these surgeries are primarily reserved for women with a known or suspected genetic predisposition to breast cancer. With the demonstration that tamoxifen can reduce breast cancer risk by almost half, chemoprevention became an option for women at increased risk for the disease. However, tamoxifen is not without risks, and it has not been widely accepted by primary care physicians. As a result, utilization of this drug has been limited. With the demonstration that raloxifene is equivalent to tamoxifen in reducing breast cancer risk, postmenopausal women at increased risk for breast cancer now have choices for breast cancer chemoprevention. Counseling is imperative so that women understand the potential risks and benefits of each prevention option and can make an informed decision. As primary prevention has evolved, so too has breast cancer screening; screening recommendations, like prevention recommendations, are now risk based. Diagnostic algorithms are available for the management of clinical and mammographic abnormalities. A key component of the diagnostic evaluation is establishing concordance between diagnostic imaging and pathologic findings, initial clinical examination, and level of suspicion.

## Introduction

The Cancer Prevention Center at M. D. Anderson Cancer Center offers a comprehensive array of clinical services and conducts research in the areas of breast, cervical, endometrial, ovarian, prostate, colorectal, skin, lung, and head and neck cancers. Programs include cancer risk assessment, including genetic counseling and testing, risk reduction counseling (promotion of a healthy lifestyle), nutrition counseling, tobacco cessation programs, chemoprevention, and cancer screening. The Cancer Prevention Center strives to address the cancer concerns of both individuals at average risk for cancer and individuals at increased risk. The Cancer Prevention Center serves as a gateway into M. D. Anderson and serves as one of M. D. Anderson's links between healthy individuals and those affected by cancer.

The Cancer Prevention Center's breast cancer prevention program provides risk assessment services, including breast and ovarian cancer genetic counseling and testing, risk reduction counseling, chemoprevention, and screening. Diagnostic services for individuals with undiagnosed breast abnormalities are also offered. In addition, two programs have been developed for patients who already have breast cancer. One program provides screening for second primary tumors in appropriately selected breast cancer patients undergoing active treatment, with an emphasis on sites of increased risk determined on the basis of the history of breast cancer and the treatment. The other program combines surveillance for recurrent breast cancer with screening for second primary tumors in selected breast cancer survivors.

## Epidemiology

Excluding cancers of the skin, breast cancer is the most common cancer among women, accounting for nearly one of every three cancers diagnosed in American women. The United States has the highest crude and age-standardized breast cancer incidences in the world: approximately 178,480 new cases of invasive breast cancer and 62,030 new cases of in situ breast cancer, 85% of which will be ductal carcinoma in situ (DCIS), were expected to be diagnosed among American women in 2007 (American Cancer Society, 2007).

Trends in the incidence of invasive breast cancer since 1975, when broad surveillance for breast cancer began, can be divided into three distinct phases. From 1975 to 1980, the incidence was essentially constant. Between 1980 and 1987, the incidence of invasive breast cancer increased 4% per year. Between 1987 and 2002, the incidence of invasive breast cancer increased by 0.3% per year (Figure 2–1). Much of the long-term increase was due to the gradual increase in the prevalence of underlying risk factors for breast cancer, such as delayed childbearing and lower parity. The

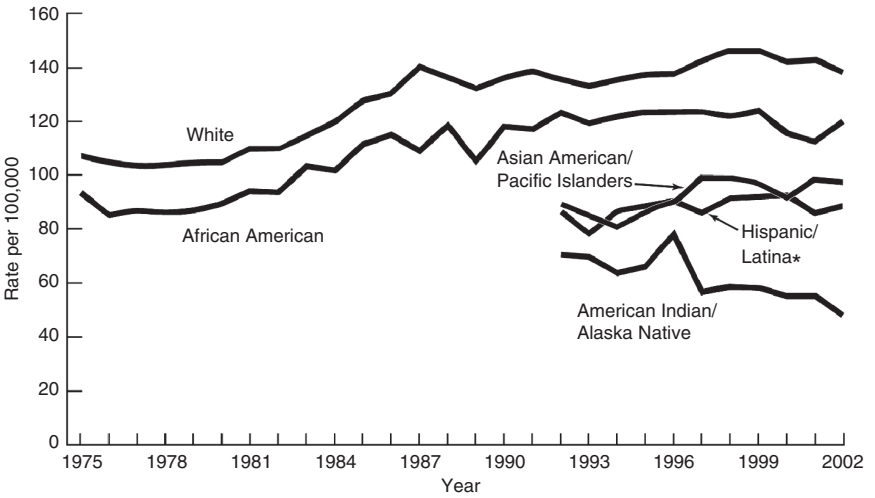


**Figure 2–1.** Trends in female breast cancer incidence rates by race and ethnicity, US (SEER), 1975–2002. Rates are age-adjusted to the 2000 US standard population. *Incidence data do not include cases from Detroit, Hawaii, Alaska Native Registry, and rural Georgia. Data source: Surveillance, Epidemiology, and End Results Program, 1973–2002, Division of Cancer Control and Population Science, National Cancer Institute, 2005.

increase seen between 1980 and 1987 was also a direct result of mammographic screening practices. The continued, but slight, increase seen after 1987 may reflect increases in the use of mammography, in the prevalence of obesity, and in the use of hormone replacement therapy.

The incidence of in situ breast cancer has increased rapidly since 1980, largely as a result of mammographic screening.

Breast cancer is the second leading cause of cancer deaths in women; 40,460 American women were expected to die of this disease in 2007 (American Cancer Society, 2007). Between 1975 and 1990, the breast cancer mortality rate increased slightly, by 0.4% annually. Between 1990 and 2002, the breast cancer mortality rate declined by an average of 2.3% per year in all women combined, with larger decreases observed in younger women (younger than 50 years) (Figure 2–2). This decline in breast cancer mortality has been attributed both to improvements in breast cancer treatment and to the benefits of mammographic screening. As the percentage of cases diagnosed at the in situ or early invasive stages of disease increases, death rates should continue to decline.

An important paradox is the difference in breast cancer incidence and mortality rates between white and African American women (Figures 2–1 and 2–2). The incidence is 20% higher in white women than in African American women. However, beginning in the early 1980s, African American women began having a higher death rate from breast cancer than white women,

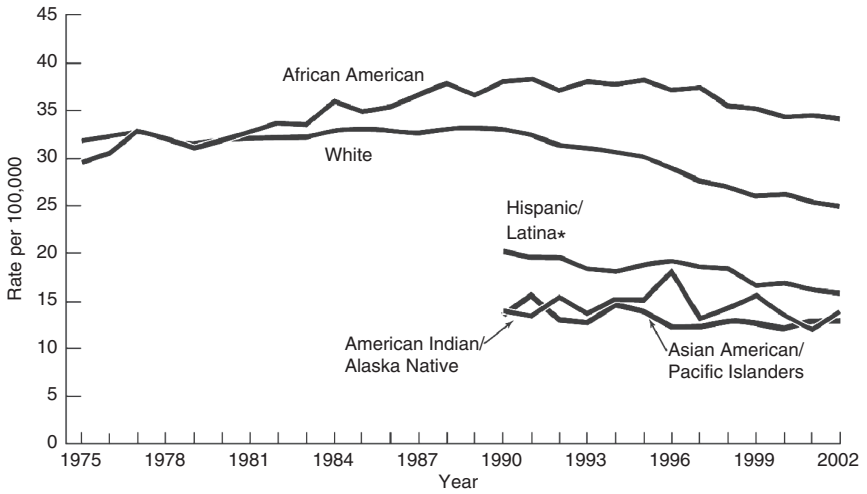


**Figure 2–2.** Trends in female breast cancer death rates by race and ethnicity, US, 1975–2002. Rates are age-adjusted to the 2000 US standard population. *Information is included for all states except Connecticut, Maine, Maryland, Minnesota, New Hampshire, New York, North Dakota, Oklahoma, and Vermont. Data source: National Center for Health Statistics, Centers for Disease Control and Prevention, 2005.

and by 2002, the death rate was 37% higher for African American women. This higher mortality rate in black women has primarily been attributed to inadequate screening practices in this population, which lead to delayed diagnosis and later-stage disease at diagnosis. However, even when black and white women are compared stage for stage, the mortality in African American women is higher. The reasons for this disparity are unknown but suggest a fundamental difference in the biology of breast cancer between African American and white women.

## Risk Factors

There are a number of established and potential risk factors for breast cancer. These can be divided into seven broad categories: age, family history of breast cancer, hormonal factors, proliferative breast disease, irradiation of the breast region at an early age, personal history of malignancy, and lifestyle factors.

### Age

Besides female sex, increasing age is the single most important risk factor for developing breast cancer. The greatest portion of a woman's lifetime risk of developing breast cancer is due to the risks at older ages (Table 2–1).

**Table 2–1. Age-Specific Probabilities of Developing Breast Cancer (Reprinted with permission from American Cancer Society, 2005.)**

| *If Current Age Is* | *The Probability of Developing Breast Cancer in the Next 10 Years Is*[a] | *Or 1 in* |
|---|---|---|
| 20 | 0.05% | 1,985 |
| 30 | 0.44% | 229 |
| 40 | 1.46% | 68 |
| 50 | 2.73% | 37 |
| 60 | 3.82% | 26 |
| 70 | 4.14% | 24 |
| Lifetime risk | 13.22% | |

Among those free of cancer at beginning of age interval. Based on cases diagnosed 2000–2002. Percentages and "1 in" numbers may not be numerically equivalent due to rounding.
[a]Probability derived using NCI DevCan software, version 6.0.
American Cancer Society, Surveillance Research, 2005.

Older women, who are at greatest risk, are the least likely to know that older age is a risk factor for breast cancer. In contrast, women younger than 50 years of age are the most likely to overestimate their breast cancer risk and the benefits of breast cancer screening.

### Family History of Breast Cancer

Women with a family history of breast cancer, especially breast cancer in a first-degree relative (i.e., mother, sister, or daughter), have an increased risk of developing breast cancer themselves. The risk is even greater if more than one first-degree relative had breast cancer, if the breast cancer occurred before menopause, or if it was bilateral. Table 2–2 shows the relative risks associated with having a first-degree relative with breast cancer. The relative risk ranges from 1.5 for postmenopausal, unilateral breast cancer to 9.0 for premenopausal, bilateral breast cancer.

Approximately 5–10% of breast cancer cases result from inherited mutations in breast cancer susceptibility genes, such as BRCA1 and BRCA2. (For more information about genetic factors, see Chapter 3.) It is very important to identify individuals who may have a genetic predisposition to breast cancer (Table 2–3) because these individuals may have a 40–60% lifetime risk of breast cancer—and in some families as high as an 80% lifetime risk —and thus have unique primary prevention and screening needs.

### Hormonal Factors

For many years, certain reproductive characteristics have been associated with an increased risk of breast cancer. Early menarche (before 12 years of age), late menopause (at or after 55 years of age), late age at first full-term pregnancy (35 years or older), and nulliparity all increase a woman's risk of breast cancer by affecting endogenous reproductive hormones. The fact

**Table 2–2. Determinants of Breast Cancer Risk (Modified from Marchant, 1997. Reprinted with permission.)**

| *Factor* | *Relative Risk* |
|---|---|
| Family history of breast cancer | |
| First-degree relative | 1.8 |
| Premenopausal first-degree relative, unilateral breast cancer | 3.0 |
| Postmenopausal first-degree relative, unilateral breast cancer | 1.5 |
| Premenopausal first-degree relative, bilateral breast cancer | 9.0 |
| Postmenopausal first-degree relative, bilateral breast cancer | 4.0–5.4 |
| Menstrual history | |
| Menarche before age 12 years | 1.7–3.4 |
| Menarche after age 17 years | 0.3 |
| Menopause before age 45 years | 0.5–0.7 |
| Menopause at age 45–54 years | 1.0 |
| Menopause at or after age 55 years | 1.5 |
| Menopause at or after age 55 years with more than 40 menstrual years | 2.5–5.0 |
| Oophorectomy before age 35 years | 0.4 |
| Anovulatory menstrual cycles | 2.0–4.0 |
| Pregnancy history | |
| Term pregnancy before age 20 years | 0.4 |
| First term pregnancy at age 20–34 years | 1.0 |
| First term pregnancy at or after age 35 years | 1.5–4.0 |
| Nulliparous | 1.3–4.0 |

**Table 2–3. Family History Characteristics Prompting Referral for Counseling for Genetic Predisposition to Breast Cancer at M. D. Anderson Cancer Center**

| |
|---|
| Multiple early-onset breast cancers (diagnosed before the age of 50 years) |
| Clustering of breast and/or ovarian cancer on one side of the family |
| Bilateral breast cancer or breast and ovarian cancer in the same individual |
| Male breast cancer |
| Ashkenazi Jewish ancestry and a family history of breast and/or ovarian cancer |
| Multiple individuals diagnosed with cancers at ages earlier than normally expected in addition to a family member with breast cancer |
| Individuals with unusual skin findings (bumps on face or hands, pigmented spots on lips, bumpy tongue) and a history of breast cancer |

that oophorectomy in women younger than 35 years is associated with a reduction in breast cancer risk of as much as 60% provides further support for the role of hormones in the development of breast cancer (Table 2–2).

Increased breast mammographic density and increased bone mineral density are also associated with increased breast cancer risk, most likely

in large part because these factors serve as physiologic measures of endogenous hormone levels.

Exogenous hormone use has also been linked to increased breast cancer risk, although this link is more controversial. Findings from an analysis of worldwide epidemiologic data showed that women who were current or recent users of birth control pills had a slightly elevated risk of developing breast cancer (Collaborative Group, 1996). This risk seemed to disappear 10 years after the therapy was discontinued. In contrast, the more recent findings from the Women's Contraceptive and Reproductive Experiences trial indicated that current and former users of oral contraceptives did not have an increased risk of developing breast cancer (Marchbanks et al., 2002).

Findings from the Women's Health Initiative randomized trial (Chlebowski et al., 2003) have helped clinicians better understand the risks and benefits of exogenous hormone use in postmenopausal women. In one arm of that trial, postmenopausal women with an intact uterus were randomly assigned to placebo or the combination of estrogen and progesterone. Estrogen plus progesterone—specifically, the combination marketed as PremPro—increased the risk of developing breast cancer by 24% (245 vs. 185 cases; hazard ratio, 1.24; weighted $P < .001$). Of greater concern, women receiving estrogen plus progesterone were more likely to be diagnosed with a breast cancer at a more advanced stage. Although the reason for this is not understood, one hypothesis is that the breasts of women receiving estrogen plus progesterone are mammographically denser (dense breasts may hinder the early detection of breast cancer).

In a second arm of the Women's Health Initiative trial (Anderson et al., 2004), women who had undergone a hysterectomy were randomly assigned to receive estrogen, specifically Premarin, or placebo. In contrast to the results in the estrogen-plus-progesterone arm, no increase in breast cancer risk was seen with the use of estrogen alone. In fact, a nonsignificant trend toward breast cancer risk reduction was observed in the women receiving Premarin.

In an analysis of the risks of endometrial and breast cancers in women with an intact uterus, the use of estrogen plus progesterone caused a greater increase in total cancer incidence than did the use of estrogen alone (Beral et al., 2005). Specifically, although endometrial cancer incidence was lower in women who received estrogen plus progesterone than in women who received estrogen alone, breast cancer incidence was higher in women who received estrogen plus progesterone than in those who received estrogen alone, such that the total cancer incidence was higher in the estrogen-plus-progesterone group. In a woman with an intact uterus, clinical decision-making is especially complex because the risk of breast cancer from combination estrogen-plus-progestin therapy must be weighed against the increased risk of endometrial cancer from the use of unopposed estrogen.

### Proliferative Breast Disease

Some women with a history of breast biopsy for benign breast disease have an increased risk of breast cancer. The degree of increase in risk depends on the specific epithelial abnormality (Table 2–4). The majority of benign breast lesions do not exhibit proliferative changes and are not associated with an increase in breast cancer risk. Proliferative lesions without atypia are associated with a twofold increase in risk. Proliferative lesions with atypia (atypical ductal or lobular hyperplasia) confer a fivefold increase in risk. The addition of a first-degree relative with breast cancer to the risk profile of atypical hyperplasia doubles the relative risk to tenfold, which is similar to the risk conferred by lobular carcinoma in situ (LCIS).

### Irradiation of the Breast Region at an Early Age

As the population of pediatric cancer survivors ages, evidence is emerging that therapeutic irradiation of the breast region during the first, second, and third decades of life increases the risk of breast cancer. The greatest risk is seen in individuals treated with radiation therapy before age 15 years; some studies suggest as great as a 35% increased risk of breast cancer in such individuals by age 40 years. Breast cancer screening practices may need to be instituted earlier in this population than is recommended for women in the general population.

### Personal History of Malignancy

It is well established that a personal history of breast cancer increases the risk of a subsequent breast cancer. In addition, a personal history of

**Table 2–4. Breast Lesions and Relative Risk for Invasive Breast Cancer (Reprinted with permission from Howell, 1995.)**

| *No Increased Risk* | *Slightly Increased Risk (1.5–2.0 Times)* | *Moderately Increased Risk (5 Times)* | *Markedly Increased Risk (10 Times)* |
|---|---|---|---|
| Adenosis | Hyperplasia (moderate or florid solid or papillary) | Atypical hyperplasia (ductal or lobular) | Lobular carcinoma in situ |
| Apocrine metaplasia | Papillomatosis | | Atypical hyperplasia with family history of breast cancer |
| Cysts | | | |
| Duct ectasia | | | |
| Fibroadenoma | | | |
| Fibrosis | | | |
| Hyperplasia (mild) | | | |
| Mastitis | | | |
| Squamous metaplasia | | | |

another malignancy, such as endometrial, ovarian, or colon cancer, may increase the risk of developing breast cancer.

### Lifestyle Factors

Epidemiologic studies have identified a number of lifestyle factors that may influence breast cancer risk.

Diet and nutrition are controversial factors. Dietary fat has received a great deal of attention as a possible risk factor for breast cancer because of the high correlation between national per capita fat consumption and the incidence of the disease. In addition, a number of experiments in laboratory animals have suggested a link between the amount and type of dietary lipids and the growth of mammary tumors. However, studies addressing this issue have produced conflicting results. Even greater uncertainty persists regarding overall dietary intake and dietary supplements, such as soy, which has been suggested to both increase and decrease breast cancer risk. Until long-term, prospective studies that include more accurate and reliable assessments of dietary intake and supplementation are conducted, no definitive statements can be made regarding diet and nutrition and breast cancer risk.

Because excess weight and weight gain are modifiable risk factors, a significant amount of interest and study has focused on the relationship between weight and breast cancer risk. Several prospective and case-control studies found an association between obesity and breast cancer risk. In other studies, the relationship between body size and risk of breast cancer differed according to menopausal status. Postmenopausal obesity and weight gain have been suggested to be associated with an increase in breast cancer risk.

A variety of other lifestyle factors have also been investigated to determine whether they increase the risk of breast cancer. A slight increase in breast cancer risk was observed in women who reported consuming at least one alcoholic beverage per day, compared with nondrinkers, and the increase was linear with each 10-gram-per-day increase in consumption. Current evidence suggests that cigarette smoking does not influence breast cancer risk except possibly in women who are slow acetylators of aromatic amines. Epidemiologic studies have demonstrated an increase in breast cancer incidence in women with a higher level of education or higher socioeconomic status, possibly related to delayed childbearing and lower parity. Silicone implants and abortion do not appear to be associated with increased risk. Breast-feeding may confer some protective effect against premenopausal breast cancer.

## Risk Assessment

Several mathematical models have been developed to predict the risk of developing breast cancer. The most commonly used models are several hereditary models, which assess genetic and familial risk of breast cancer, and the Gail

model, which assesses populational risk using nongenetic factors. Specifics of the models for hereditary predisposition are reviewed in Chapter 3.

Risk factors included in the Gail model are age, age at menarche, age at first live birth (or nulliparity), family history of breast cancer in first-degree relatives, history of breast biopsy, and history of breast biopsy revealing atypical hyperplasia (Gail et al., 1989). Because the incidence of breast cancer differs by race, the current, modified version of the Gail model includes race-specific data. This modified version of the Gail model was used in the Breast Cancer Prevention Trial (BCPT) and the Study of Tamoxifen and Raloxifene for the Prevention of Breast Cancer (STAR). The model accurately predicted the number of invasive breast cancers in the placebo arm of the BCPT: overall, the model predicted 159 cases of invasive breast cancer in the trial, and 155 cases were observed, yielding an expected-to-observed ratio close to unity (1.03).

After the announcement of the results of the BCPT in 1998 and the subsequent validation of the modified Gail model, the National Cancer Institute (NCI) developed and distributed a computer program based on the Gail model, the Breast Cancer Risk Assessment Tool, for calculating the projected risk of developing breast cancer. This program is available online at the NCI Web site and at www.breastcancerprevention.com and can be used to facilitate the calculation of a woman's breast cancer risk in the clinical setting. The Breast Cancer Risk Assessment Tool is the first multifactorial model that has been developed and made available for clinicians to use for estimating the risk of a specific cancer.

The NCI program prompts the user to input information about specific breast cancer risk factors and provides a printout showing projected breast cancer risk in the next 5 years and projected lifetime risk. For comparative purposes, the printout also includes the average 5-year and lifetime risks for a woman of the same age and race as the woman evaluated.

Increased risk is defined as a 5-year projected risk of 1.7% or greater. This is the average risk of a 60-year-old woman. This risk was chosen as the cutoff point for elevated risk because 60 years was the median age at which breast cancer was diagnosed in the United States at the time the model was developed.

It is important to understand the limitations of the modified Gail model. It is not applicable to women with a personal history of invasive breast cancer, DCIS, or LCIS. In calculating breast cancer risk, the Gail model makes no adjustment for a first-degree relative with premenopausal or bilateral breast cancer. In addition, the Gail model does not include genetic mutations in the calculation of breast cancer risk. As a result, risk may be significantly underestimated. For these reasons, the risk calculation cannot be interpreted outside the context of the patient's overall personal and family history.

However, even with these limitations, the modified Gail model provides valuable information and serves as a key starting point in the evaluation of breast cancer risk. With the exception of women meeting the criteria for genetic-risk evaluation and counseling (Table 2–3), all women 35 years

of age and older who present to the Cancer Prevention Center for breast cancer screening have a risk assessment calculation performed using the modified Gail model. On the basis of the estimated risk, a unique, personal prevention program is developed. This prevention program includes recommendations for primary prevention strategies and screening appropriate to the individual's risk level.

Three variables in the modified Gail model change or may change over time: age, family history of first-degree relatives with breast cancer, and history of breast biopsy with or without atypical hyperplasia. Because incremental increases in age produce only slight increases in the 5-year breast cancer risk, recalculations to adjust for age are done only periodically, about every 5 years unless the patient just missed the 1.7% cutoff defining increased breast cancer risk, in which case the risk is recalculated annually. However, any change in the other two variables—a new breast cancer in a first-degree relative and an interim breast biopsy—prompts recalculation because the associated increase in breast cancer risk can significantly alter the benefit-versus-risk ratio for chemoprevention therapy (for more information, see the section "Chemoprevention" later in this chapter).

## Primary Prevention

Currently, three approaches have been proven to decrease breast cancer risk: prophylactic oophorectomy, prophylactic mastectomy, and chemoprevention with tamoxifen or raloxifene. Prophylactic surgery should be considered only by women with a known or suspected genetic predisposition or a calculated breast cancer risk similar to that of women with a genetic predisposition. In contrast, chemoprevention may be considered by any woman at increased risk for breast cancer. Lifestyle modifications have not been definitively proven to reduce the risk of developing breast cancer, but because they can lead to better health, counseling about lifestyle modifications is nevertheless an important element of primary breast cancer prevention.

### Lifestyle Modification

Studies exploring whether modification of lifestyle factors can reduce breast cancer risk have yielded inconsistent and controversial findings. However, regardless of their impact on breast cancer risk, lifestyle modifications can lead to better health and are recommended for individuals at all risk levels. These modifications include switching to a healthy diet with an emphasis on plant sources, adopting a physically active lifestyle, achieving a healthful weight and maintaining it throughout life, limiting alcohol intake, and avoiding smoking.

For women at average risk for breast cancer, the benefits of preventing an unwanted pregnancy are felt to outweigh the potential risks of oral

contraceptives. Conversely, women at very high risk for breast cancer (i.e., carriers of genetic mutations predisposing to breast cancer development) are probably well advised to consider nonhormonal forms of contraception.

Women considering hormone replacement therapy (estrogen alone or estrogen plus progesterone) need to carefully weigh the benefits against the risks. In addition, women should be counseled about nonhormonal alternative therapies for the management of menopausal symptoms.

### Prophylactic Oophorectomy

Oophorectomy in women younger than 35 years of age has been shown to reduce the risk of breast cancer by as much as 60%. However, surgically induced menopause at this age is associated with its own risks. In the postmenopausal period, osteoporosis escalates and there is an increased risk of cardiovascular disease. In addition, women with premature menopause can have a variety of associated symptoms that must be managed—for example, hot flashes, night sweats, vaginal dryness, and mood changes. For these reasons, prophylactic oophorectomy is typically considered only for women with BRCA1 or BRCA2 mutations, in whom the potential benefits of this procedure are increased because of the substantial reduction not only in breast cancer risk but also in ovarian cancer risk.

### Prophylactic Mastectomy

Prophylactic mastectomy (see Chapter 7) is an aggressive surgical procedure with many physiological and psychological ramifications. For most women at increased risk for breast cancer, the drawbacks of prophylactic mastectomy outweigh the benefits, and the procedure is therefore not appropriate. However, for women with a considerable risk of developing breast cancer—primarily women with a genetic predisposition but also, to a lesser extent, women with LCIS—prophylactic mastectomy remains a risk reduction strategy to be considered. This is especially true given the 90% reduction in breast cancer incidence seen after bilateral prophylactic mastectomy in women at moderate to high risk (Hartmann et al., 1999). Prophylactic mastectomy should be undertaken only after extensive counseling so that the patient has a thorough understanding of her breast cancer risk and other available risk reduction strategies and the psychological issues associated with the procedure. In addition, because total mastectomy, without preservation of the nipple–areolar complex, is the current procedure of choice, the availability of immediate breast reconstruction should be discussed during the counseling process. There is currently no role for subcutaneous mastectomy in the primary prevention of breast cancer.

It is an interesting paradox that prophylactic mastectomy is considered as a breast cancer prevention strategy while women diagnosed with breast cancer are given the option of breast conservation therapy. Because

of advances in breast cancer chemoprevention, most breast cancer prevention experts are shifting the emphasis away from prophylactic surgery toward chemoprevention, especially for patients with LCIS. In the current M. D. Anderson practice algorithm, patients with LCIS are seen in the Cancer Prevention Center for risk counseling and a review of the currently available primary prevention strategies, especially chemoprevention. Patients with LCIS are referred to a surgeon only if they are seriously considering and desiring prophylactic mastectomy.

## Chemoprevention

With the publication of the findings of the landmark BCPT in 1998 (Fisher et al., 1998), chemoprevention of breast cancer emerged as a risk reduction strategy for women at increased risk for the disease. Since the unblinding of STAR in 2006 (Vogel et al., 2006), postmenopausal women have had a choice of either tamoxifen or raloxifene for risk reduction.

### *Tamoxifen*

Tamoxifen citrate is a selective estrogen receptor modulator that competes with circulating estrogen for binding to the estrogen receptor. Depending on the tissue and species, tamoxifen acts as an estrogen agonist or an estrogen antagonist.

For more than 20 years, tamoxifen has been used in the treatment of breast cancer. Tamoxifen was chosen as a potential breast cancer chemopreventive agent because studies showed that tamoxifen given for 5 years reduced the incidence of recurrent breast cancer by 42% and reduced the incidence of contralateral breast cancer by 47%.

In 1992, the National Surgical Adjuvant Breast and Bowel Project, with the support of the NCI, launched the landmark BCPT, also known as the P-1 trial or the tamoxifen prevention trial, to investigate the value of tamoxifen in reducing the risk of primary invasive breast cancer in women at increased risk for the disease (Fisher et al., 1998). A total of 13,388 women aged 35 years or older who were at increased risk for breast cancer were entered into the trial and randomly assigned to receive either tamoxifen 20 mg daily or placebo daily for 5 years. Increased risk was defined as a personal history of LCIS, a 5-year risk of developing breast cancer of at least 1.7% as calculated using the modified Gail model, or age 60 years or older.

Tamoxifen reduced the risk of developing invasive breast cancer by 49%. As can be seen from Table 2–5, the risk reduction was seen for all age groups and all projected levels of risk. Women with a history of LCIS had a 56% risk reduction, and women with a history of atypical hyperplasia had a dramatic 86% risk reduction. The incidence of estrogen receptor–positive tumors was 69% lower in the tamoxifen group than in the placebo group; however, the rate of estrogen receptor–negative tumors was not

**Table 2–5. Average Annual Rates for Outcomes in the Breast Cancer Prevention Trial (Adapted and reprinted with permission from Fisher et al., 1998.)**

| | *Rate per 1,000 Women* | | |
|---|---|---|---|
| *Outcome* | *Tamoxifen* | *Placebo* | *Risk Ratio (95% CI)* |
| Noninvasive breast cancer | 1.35 | 2.68 | 0.50 (0.33–0.77) |
| Invasive breast cancer | 3.43 | 6.76 | 0.51 (0.39–0.66) |
| Invasive breast cancer by patient characteristic | | | |
| Age (years) | | | |
| ≤49 | 3.77 | 6.70 | 0.56 (0.37–0.85) |
| 50–59 | 3.10 | 6.28 | 0.49 (0.29–0.81) |
| ≥60 | 3.33 | 7.33 | 0.45 (0.27–0.74) |
| History of lobular carcinoma in situ | | | |
| Yes | 5.69 | 12.99 | 0.44 (0.16–1.06) |
| No | 3.30 | 6.41 | 0.51 (0.39–0.68) |
| History of atypical hyperplasia | | | |
| Yes | 1.43 | 10.11 | 0.14 (0.03–0.47) |
| No | 3.61 | 6.44 | 0.56 (0.42–0.73) |
| No. of first-degree relatives with breast cancer | | | |
| 0 | 2.97 | 6.45 | 0.46 (0.24–0.84) |
| 1 | 3.03 | 6.00 | 0.51 (0.35–0.73) |
| 2 | 4.75 | 8.68 | 0.55 (0.30–0.97) |
| ≥3 | 7.02 | 13.72 | 0.51 (0.15–1.55) |
| 5-year predicted breast cancer risk (%) | | | |
| ≤2.00 | 2.06 | 5.54 | 0.37 (0.18–0.72) |
| 2.01–3.00 | 3.51 | 5.18 | 0.68 (0.41–1.11) |
| 3.01–5.00 | 3.88 | 5.88 | 0.66 (0.39–1.09) |
| ≥5.01 | 4.52 | 13.28 | 0.34 (0.19–0.58) |
| Invasive endometrial cancer | | | |
| Overall | 2.30 | 0.91 | 2.53 (1.35–4.97) |
| Age ≤ 49 years | 1.32 | 1.09 | 1.21 (0.41–3.60) |
| Age ≥ 50 years | 3.05 | 0.76 | 4.01 (1.70–10.90) |
| Fractures | | | |
| Hip | 0.46 | 0.84 | 0.55 (0.25–1.15) |
| Hip, spine, and lower radius combined | 4.29 | 5.28 | 0.81 (0.63–1.05) |
| Thromboembolic events | | | |
| Stroke | 1.45 | 0.92 | 1.59 (0.93–2.77) |
| Transient ischemic attack | 0.73 | 0.96 | 0.76 (0.40–1.44) |
| Pulmonary embolism | 0.69 | 0.23 | 3.01 (1.15–9.27) |
| Deep vein thrombosis | 1.34 | 0.84 | 1.60 (0.91–2.86) |
| Cataracts | | | |
| Developed cataracts | 24.82 | 21.72 | 1.14 (1.01–1.29) |
| Developed cataracts and underwent cataract surgery | 4.72 | 3.00 | 1.57 (1.16–2.14) |

*Abbreviation*: CI, confidence interval.

significantly different between the two groups. An additional benefit of tamoxifen suggested in the BCPT was a reduction in the incidence of osteoporotic fractures.

Tamoxifen is not without risks: the BCPT showed that tamoxifen was associated with increased risks of endometrial cancer, venous thromboembolic events, cataract development, and the need for cataract surgery (Table 2–5). These risks were present for all women in the trial but were increased only in women over the age of 50 years. Common side effects reported included bothersome hot flashes and bothersome vaginal discharge. Tamoxifen was not associated with weight gain or depression.

Since the unblinding of the BCPT, the findings of other tamoxifen prevention trials have been published: the Italian Tamoxifen Prevention Study (Veronesi et al., 1998), the Royal Marsden Hospital tamoxifen randomized prevention trial (Powles et al., 1998), and the International Breast Cancer Intervention Study, or IBIS-1 (Cuzick et al., 2002). The Italian and Royal Marsden trials showed no benefit of tamoxifen over placebo in terms of reducing the incidence of breast cancer. The difference between the results of these two trials and those of the BCPT are most likely due to differences in study population (e.g., lower risk) and trial design. The IBIS-1 trial showed a 33% reduction in the incidence of breast cancer with tamoxifen, confirming the breast cancer risk reduction benefit that was seen in the BCPT. A meta-analysis of all the tamoxifen prevention studies demonstrated that tamoxifen reduced the risk of breast cancer by 38% and confirmed the serious risks of endometrial cancer and venous thromboembolic events (Cuzick et al., 2003).

Since 1998, tamoxifen has been approved by the Food and Drug Administration for breast cancer risk reduction. However, despite the significant breast cancer risk reduction conferred by tamoxifen, tamoxifen for risk reduction has not been widely accepted by primary care physicians, and therefore many women at increased risk for breast cancer are never offered the drug for chemoprevention. Not only the risks of tamoxifen therapy but also the fact that tamoxifen is a well-recognized breast cancer "treatment" most likely are what make primary care physicians reluctant to prescribe tamoxifen to healthy women at increased risk for breast cancer.

### *Raloxifene*

Raloxifene is a second-generation selective estrogen receptor modulator. It was initially approved by the Food and Drug Administration for prevention and treatment of osteoporosis, following publication of results of the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, which demonstrated a reduction in the incidence of fractures and an increase in bone density with the use of raloxifene in postmenopausal women with osteoporosis.

The development of breast cancer was a secondary endpoint of the MORE trial. A separate analysis demonstrated that the incidence of breast cancer was 76% lower with raloxifene than with placebo (Cummings et al., 1999). Similar to the findings with tamoxifen, raloxifene was associated with an increase in the incidence of venous thromboembolic events. In contrast to the findings with tamoxifen, raloxifene was not associated with an increase in the incidence of endometrial cancer. However, the follow-up from the MORE study was too short to permit definitive judgment about this relationship, especially given that it took nearly a decade for the effects of tamoxifen on the endometrium to be fully understood.

The intriguing findings from the MORE study served as the basis for STAR (Vogel et al., 2006). Opened in May 1999, STAR enrolled 19,747 postmenopausal women at increased risk for breast cancer. Women were randomly assigned to receive either tamoxifen 20 mg daily or raloxifene 60 mg daily for 5 years.

At the unblinding of the trial in April 2006, raloxifene was found to be equivalent to tamoxifen in reducing the risk of invasive breast cancer development in postmenopausal women at increased risk for the disease (Table 2–6). Both drugs reduced the risk of breast cancer by about 50%. While tamoxifen has been shown to reduce the incidence of LCIS and DCIS, raloxifene did not have an effect on the incidence of these

**Table 2–6. Outcomes in the Study of Tamoxifen and Raloxifene (Adapted from Vogel et al., 2006.)**

| | *No. of Events* | | |
|---|---|---|---|
| *Outcome* | *Tamoxifen* | *Raloxifene* | *Risk Ratio (95% CI)* |
| Invasive breast cancer | 163 | 168 | 1.02 (0.82–1.28) |
| Noninvasive breast cancer | 57 | 80 | 1.40 (0.98–2.00) |
| Invasive uterine cancer | 36 | 23 | 0.62 (0.35–1.08) |
| Uterine hyperplasia | 84 | 14 | 0.16 (0.09–0.29) |
| Hyperplasia with atypia | 12 | 1 | 0.08 (0.00–0.55) |
| Hyperplasia without atypia | 72 | 13 | 0.18 (0.09–0.32) |
| Hysterectomy during follow-up[a] | 244 | 111 | 0.44 (0.35–0.56) |
| Pulmonary embolism (PE) | 54 | 35 | 0.64 (0.41–1.00) |
| Deep vein thrombosis (DVT) | 87 | 65 | 0.74 (0.53–1.03) |
| PE and DVT combined | 141 | 100 | 0.70 (0.54–0.91) |
| Stroke | 53 | 51 | 0.96 (0.64–1.43) |
| Fractures | 104 | 96 | 0.92 (0.69–1.22) |
| Developed cataracts during follow-up | 394 | 313 | 0.79 (0.68–0.92) |
| Developed cataracts and had cataract surgery | 260 | 215 | 0.82 (0.68–0.99) |

*Abbreviation*: CI, confidence interval.

[a]Among women not diagnosed with uterine cancer.

diseases. This result confirmed results reported in 2004 from the Continuing Outcomes Relevant to Evista trial, a 4-year extension of the MORE trial designed to further assess the effect of raloxifene on breast cancer (Martino et al., 2004).

In STAR, the incidence of bone fractures was equivalent in the tamoxifene and raloxifene groups. As previously noted, raloxifene is approved by the Food and Drug Administration for the prevention and treatment of osteoporosis.

Of great interest in understanding the risks of raloxifene and tamoxifen is examining how these two drugs compared with respect to the incidence of uterine cancer. The fact that more than half of the women who joined STAR had a history of a hysterectomy and therefore were not at risk for uterine cancer indicates that both potential participants and investigators were using the risk-benefit profile of tamoxifen as the basis for determining which women might obtain benefit from participating in the study. The large proportion of STAR participants who had undergone hysterectomy before trial entry limited the investigators' ability to assess differences in the effects of raloxifene and tamoxifen on the incidence of uterine cancer. The incidence of uterine cancer was 38% lower in the raloxifene arm. There were a total of 59 uterine cancers, 36 among women taking tamoxifen and 23 among women taking raloxifene (relative risk, 0.62; 95% confidence interval, 0.35–1.08). While the finding was not statistically significant, it was not clinically insignificant. There was a statistically significant difference between the groups in the incidence of uterine hyperplasia (with and without atypia)—this finding was 84% less common in the raloxifene arm, suggesting that uterine cancer is not stimulated by raloxifene. This resulted in more hysterectomies being performed in the tamoxifen group, which obscured the difference in the effect of raloxifene and tamoxifen on the development of uterine cancer. These findings provide further evidence that raloxifene does not have the same effect as tamoxifen on the uterus.

The incidence of deep vein thrombosis and pulmonary embolism was 30% lower in the raloxifene arm than in the tamoxifen arm, a statistically significant finding. The incidences of strokes and transient ischemic attacks were statistically equivalent in the two arms; there was no difference between the arms in the incidence of death from strokes. Women at increased risk for stroke (those with uncontrolled hypertension, uncontrolled diabetes, or a history of stroke, transient ischemic attack, or atrial fibrillation) were not eligible to participate in STAR. The incidence of heart attacks was also equivalent in the two arms.

Both the incidence of cataracts and the incidence of cataract surgery were significantly less common in the raloxifene group.

Side effects of both tamoxifen and raloxifene were mild to moderate in severity, and quality of life was the same for the two drugs. Women receiving tamoxifen reported more vasomotor symptoms, vaginal discharge,

vaginal bleeding, genital itching or irritation, difficulty with urinary bladder control, and leg cramps. Women receiving raloxifene reported more vaginal dryness, pain with intercourse, and weight gain.

Now that the results of STAR have shown that raloxifene is effective and safe for breast cancer prevention, postmenopausal women have two options for reducing their risk of developing breast cancer. While the BCPT was landmark in that it was the first randomized trial to demonstrate that a drug could reduce the incidence of breast cancer, STAR is anticipated to have a greater impact on clinical practice. As previously noted, tamoxifen has not been widely accepted by primary care physicians. However, raloxifene is well accepted not only by primary care physicians but also by women. With the new finding of raloxifene's breast cancer benefit, we now have a drug that simultaneously reduces the risk of two diseases of concern to women: breast cancer and osteoporosis.

### *Counseling before Initiation of Therapy*

Women who are found to be at increased risk for breast cancer—women with a personal history of LCIS or a 5-year breast cancer risk of 1.7% or greater according to the modified Gail model—should be counseled regarding the benefits and risks of risk reduction therapy. Women with a 5-year predicted breast cancer risk of less than 1.7% are unlikely to obtain sufficient breast cancer risk reduction benefit from tamoxifen or raloxifene therapy to outweigh the risks associated with these therapies. As previously noted, risk should be reassessed periodically, especially if any significant change occurs in breast cancer risk factors.

For any individual woman at increased risk for breast cancer, an attempt must be made to predict whether the net benefit of risk reduction therapy will outweigh the net risk. The net benefit is primarily a function of the woman's predicted breast cancer and osteoporosis risks—the greater a woman's risks of breast cancer and osteoporosis, the greater the benefit of risk reduction therapy. (Of note, although tamoxifen and raloxifene were equivalent in reducing osteoporotic fractures, only raloxifene is approved by the Food and Drug Administration for this use.) Risk reduction therapy with either tamoxifen or raloxifene reduces the risk of breast cancer by approximately 50%, and the magnitude of this benefit increases as a direct function of increasing 5-year predicted breast cancer risk.

The net risk of risk reduction therapy is a function of the particular drug chosen and the woman's age, race, and hysterectomy status. For any given combination of race and drug, the magnitude of the expected effect, be it beneficial or harmful, increases as a direct function of increasing age (Table 2–7). For example, a 60-year-old white woman has a higher risk of a vascular event than does a 40-year-old white woman.

**Table 2–7. Annual Incidence Rates per 1,000 Woman-Years for Adverse Events in the Absence of Risk Reduction Therapy (Adapted from Gail et al., 1999.)**

| | *Rates for White Women of Ages* | | | | *Rates for Black Women of Ages* | | | |
|---|---|---|---|---|---|---|---|---|
| *Event* | *40–49 years* | *50–59 years* | *60–69 years* | *70–79 years* | *40–49 years* | *50–59 years* | *60–69 years* | *70–79 years* |
| Stroke[a] | 0.45 | 1.10 | 3.25 | 7.50 | 1.26 | 3.19 | 7.48 | 9.00 |
| Pulmonary embolism[b] | 0.15 | 0.50 | 0.88 | 1.93 | 0.46 | 1.50 | 2.02 | 3.09 |
| Deep vein thrombosis[b] | 0.49 | 0.55 | 0.98 | 1.61 | 1.52 | 1.65 | 2.25 | 2.58 |
| Endometrial cancer[c] | 0.21 | 0.81 | 1.44 | 1.63 | 0.08 | 0.35 | 0.89 | 0.88 |
| Hip fracture[d] | 0.04 | 1.02 | 2.42 | 7.44 | 0.03 | 0.55 | 0.92 | 2.83 |

[a]Rates from Broderick JP, Phillips SJ, Whisnant JP, et al. Incidence rates of stroke in the eighties: the end of the decline in stroke? *Stroke* 1989;20:577–582.

[b]Rates from Silverstein MD, Heit JA, Mohr DN, et al. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med* 1998;158:585–593.

[c]1991–1995 Surveillance, Epidemiology, and End Results rates adjusted for the prevalence of intact uteri.

[d]Rates from Melton LJ, Chrischilles EA, Cooper C, et al. How many women have osteoporosis? *J Bone Mineral Res* 1992;7:1005–1010.

Race is also an important determinant of risk. For example, depending on age, the baseline rates of vascular events are 1.5–2.5 times higher among black women than among white women. Hysterectomy status also affects risk: while tamoxifen is associated with an increased risk of uterine cancer that is not seen with raloxifene, this increased risk is not an issue for women who have had a hysterectomy. Other factors may also influence the risks of therapy and must be considered in the risk calculation. For example, women who have had cataract surgery with placement of artificial lenses do not have the risk of cataracts that is associated with tamoxifen therapy.

When all the factors that affect the benefits and risks of chemoprevention are considered, it is possible to identify several groups of women in whom the positive effects of risk reduction will most likely outweigh any negative effects.

Premenopausal women at increased risk for breast cancer are candidates for tamoxifen, as they will obtain the benefits of the drug without an increase in the risks of adverse events. Raloxifene is not an option for this group, as it is not approved for premenopausal women.

In general, postmenopausal women who will obtain a significant benefit from chemoprevention are those who have a higher risk of developing breast cancer and have profiles that put them at a lower risk of adverse events. These groups include:

1. Women with a very high risk of breast cancer (i.e., a personal history of LCIS or atypical hyperplasia).
2. Women 50 years of age or older with a 5-year predicted breast cancer risk of 1.7% or more who have had a hysterectomy (if tamoxifen is being considered) and either are at low risk for vascular events (nonsmoker, not obese, not diabetic, not hypertensive, no prior history of a venous thromboembolic event, physically active) or are currently taking estrogen replacement therapy. The risk of vascular events from tamoxifen or raloxifene in this group is similar to the risk of vascular events associated with estrogen replacement therapy; thus, a change from estrogen to either risk reduction agent would not significantly increase the risk of vascular events.

Some women may be considered for risk reduction therapy even if the risk-benefit assessment indicates a negative net effect. Each individual woman will have her own perception of how the various beneficial and detrimental effects should be weighed, and consideration should be given to each woman's personal perceptions and desires. Some women who are at increased risk for breast cancer are willing to incur the potential risks of chemoprevention in exchange for the potential reduction in breast cancer risk. Health care providers should keep in mind that a woman's decision to take a drug for prevention is a personal decision. Except in extreme cases, once a woman fully understands the risks associated with chemoprevention therapy, she should not be denied the opportunity to potentially reduce her risk of breast cancer if she has a strong desire to do so.

### *Care of Women Taking Tamoxifen or Raloxifene*

Women receiving chemoprevention therapy should have follow-up visits every 6 months. Each visit should include a clinical breast examination (CBE) and symptom assessment. Women should also undergo annual screening mammography and—in women taking tamoxifen who have an intact uterus—an annual gynecologic assessment to ascertain if they have abnormal vaginal bleeding or other symptoms raising concern about uterine pathology.

Symptom assessment should include inquiries about thromboembolic or gynecologic (for tamoxifen users) symptoms. Women should be educated about such symptoms and the need to promptly report any that develop. Any abnormal vaginal bleeding should be evaluated with transvaginal sonography, endometrial biopsy, or other procedures as the clinical situation dictates. There is currently no indication for routine endometrial screening, either by transvaginal sonography or endometrial biopsy, of asymptomatic women taking tamoxifen.

The common side effects of risk reduction therapy have been well defined. Hot flashes are a common reaction, seen more frequently with tamoxifen than with raloxifene. Hot flashes are more common among women near the age of menopause and women who have just discontinued estrogen replacement therapy, but hot flashes can occur in women of any age. Nonhormonal management of hot flashes can involve vitamin E, evening primrose oil, or other over-the-counter agents or some prescription medications such as venlafaxine (Effexor), gabapentin (Neurontin), or clonidine.

Some patients experience vaginal dryness, which can be managed with nonhormonal remedies available over the counter (e.g., Astroglide, Replens). Estrogen creams should be avoided because of the sustained systemic absorption seen with such preparations. However, Estring, a slow-release estrogen vaginal ring inserted every 3 months, or Vagifem estradiol tablets, inserted intravaginally twice a week, were allowed in the BCPT and STAR.

Some patients taking tamoxifen experience a clear, nonodorous, nonirritating vaginal discharge. It is unusual for the discharge to be copious. Once other causes of vaginal discharge have been eliminated, the patient can be reassured that this discharge is associated with the tamoxifen therapy and is harmless. This discharge usually resolves after cessation of therapy.

## Screening

The National Comprehensive Cancer Network Breast Cancer Screening and Diagnosis Guidelines (available at www.nccn.org/professionals/physician_gls/PDF/breast-screening.pdf) serve as the basis for breast cancer screening recommendations in the M. D. Anderson Cancer Prevention Center. Specific breast cancer screening recommendations depend on the woman's personal risk of breast cancer.

Before screening is initiated, any severe comorbid conditions that limit life expectancy or therapeutic intervention should be considered. Screening may not be appropriate in women with a life expectancy of less than 10 years or those who could not tolerate or would not elect to pursue treatment of any identified disease.

Individuals are stratified on the basis of their predicted 5-year breast cancer risk, as determined using the modified Gail model, or on the basis of a history of thoracic radiation therapy, history of proliferative breast disease, genetic predisposition, or prior history of breast cancer. Women who do not fall into one of these risk categories are classified as average risk and undergo routine screening, which consists of CBE every 1–3 years between the ages of 20 and 39 years and annually along with screening mammography beginning at age 40. If the predicted 5-year breast cancer risk is 1.7% or greater, annual mammography and CBE every 6–12 months may be started at age 35, and risk reduction strategies should be considered.

Women who received thoracic radiation therapy during the second or early part of the third decade of life are at increased risk for breast cancer. The increase in incidence begins approximately 8–10 years after radiation therapy. For this reason, in women who received thoracic radiation therapy at a young age, CBE is recommended annually for women younger than 25 years of age. These women should also consider annual mammography and CBE every 6–12 months beginning 8–10 years after radiation therapy but not before age 25.

Guidelines for women with a known or suspected genetic predisposition are similar to guidelines for women with a history of thoracic radiation therapy except that annual screening mammography is initiated at age 25 for patients with hereditary breast and ovarian cancer syndrome or 5–10 years before the earliest age at which breast cancer was diagnosed in a family member for patients with a strong family history or other genetic predisposition, but not before age 25. Annual magnetic resonance imaging should be considered as an adjunct to mammography and CBE. Women should be counseled regarding risk reduction strategies.

Women with atypical hyperplasia or LCIS should have CBE every 6–12 months and annual mammograms from the time of diagnosis, but not before age 25, and should consider risk reduction strategies.

Instead of breast self-examination, M. D. Anderson is now focusing more on breast self-awareness. This change, although it may seem at first glance merely semantic, represents a paradigm shift from formal teaching of a technique for self-examination of the breasts to reinforcing the importance of a woman's being familiar with her breasts, however she might accomplish that, and promptly reporting any change to her physician (Bevers, 2004). This change was implemented after findings from a trial of breast self-examination conducted in Shanghai, China, showed that mortality from breast cancer was not lower in women who received intensive breast self-examination instruction than in those who received no instruction in breast self-examination (Thomas et al., 2002). Additionally, there was no apparent stage difference between the breast cancers detected in the two groups. The finding that most breast cancers were detected by women incidentally while showering or dressing further supported the approach of breast self-awareness.

## Diagnostic Evaluation of Clinical and Mammographic Breast Abnormalities

During the course of breast cancer screening, clinical and mammographic abnormalities will be identified that require further evaluation. Clinical abnormalities can be divided into four categories: dominant mass, asymmetric thickening or nodularity, nipple discharge, and skin changes. Guidelines have been developed to direct the diagnostic evaluation of both mammographic and clinical abnormalities.

### Mammographic Abnormality with Normal Findings on CBE

If the findings on mammography are abnormal, a diagnostic workup is necessary to definitively evaluate the abnormality. The American College of Radiology has established the Breast Imaging Reporting and Data System (BI-RADS) to standardize mammography reports (for more information, see Chapter 4). BI-RADS category 0 refers to mammograms for which some combination of additional mammographic views, sonography, and comparison with prior films is necessary to determine the final BI-RADS category. In the screening setting, women with mammographic findings classified as BI-RADS category 1 (normal) or 2 (benign finding) may return to routine screening. Mammographic findings classified as BI-RADS category 3, 4, or 5 necessitate additional diagnostic management.

Mammographic findings classified as BI-RADS category 4 (suspicious abnormality) or 5 (highly suggestive of malignancy) require tissue diagnosis for definitive assessment. The tissue diagnosis may be accomplished with the use of fine-needle aspiration, core needle biopsy, or excisional biopsy (more information about these techniques is provided in Chapters 4 through 7). Establishing concordance between the pathologic findings on fine-needle aspiration or core needle biopsy and the findings on diagnostic imaging is integral in determining that the area of concern has been adequately assessed. Benign pathologic findings would not be concordant with a highly suspicious mammogram. If findings are concordant, women with benign results may be followed with diagnostic mammography in 6–12 months, and women with malignant results require an oncologic referral. Findings of atypical hyperplasia or LCIS may warrant surgical excision to determine whether the lesion is benign or malignant. However, if the pathology and diagnostic imaging findings are discordant, reimaging or rebiopsy may be indicated to achieve concordance.

Women with findings classified as BI-RADS category 3 (probably benign) may reasonably be cared for with close surveillance with diagnostic mammograms every 6 months for 1–2 years. Stable lesions may permit the patient to return to routine screening; however, lesions that change over the course of surveillance require further evaluation by tissue diagnosis as just outlined. If the patient is noncompliant or highly anxious, further evaluation by tissue diagnosis may be indicated.

### Dominant Mass

The diagnostic evaluation of a dominant mass is based on the woman's age. In women 30 years of age or older, the mass should be investigated with mammography and sonography. In women under the age of 30 years, breast cancers are rare, and the sensitivity of mammography and risks associated with mammography are of concern. In women in this age group, breast sonography, direct needle biopsy, and observation are options for the initial diagnostic evaluation of the palpable finding.

Clinical suspicion plays a critical role in the approach to women under the age of 30 years who present with a dominant mass. If the risk or likelihood of malignancy is determined to be low on the basis of history and physical examination, observation of the mass for one or two menstrual cycles may be the initial approach. The patient should be reevaluated after the appropriate interval to ascertain whether the mass has resolved. Persistence of the mass necessitates further evaluation with either direct needle biopsy or breast sonography.

Direct needle biopsy, usually by fine-needle aspiration, will yield either fluid, which suggests a cyst, or a cellular aspirate. When fine-needle aspiration yields a cellular aspirate and pathologic evaluation of the aspirate suggests a fibroadenoma, a 3- to 6-month follow-up CBE is done to assess the stability of the mass. Alternatively, the lesion may be surgically excised to confirm the benign findings. Nondiagnostic or indeterminate specimens necessitate reaspiration or biopsy under ultrasound guidance. If the level of suspicion has increased, a mammogram may be indicated prior to rebiopsy. If direct needle biopsy reveals cancer, regardless of whether the biopsy yielded fluid or a cellular aspirate, a mammogram should be obtained before the patient is referred for oncologic treatment if a mammogram has not already been obtained.

When fine-needle aspiration yields fluid with benign cytologic features and results in resolution of the mass, the mass is most likely a cyst; however, a CBE should be performed in 2–4 months to ascertain that the mass has not recurred. If the mass persists after fluid is aspirated, the mass should be further investigated with mammography and sonography to rule out a suspicious intracystic mass.

Finally, a dominant mass in a woman under the age of 30 years may be evaluated with breast sonography. This is managed in the same way as a dominant mass in a woman 30 years of age or older with the exception that a mammogram is obtained prior to the sonogram for the older age group. Sonography will reveal whether the mass is solid or cystic. Fine-needle aspiration is indicated if the sonographic findings are indeterminate for a cyst or if there is uncertainty regarding concordance between the sonographic findings and the mammographic abnormality. In addition, the cyst may be aspirated if the patient is symptomatic or the cyst limits future mammographic interpretation. If sonography reveals a solid lesion with the characteristics of a fibroadenoma, the lesion can be reevaluated in 6 months with CBE and the appropriate breast imaging study to assess stability, or the lesion can be evaluated pathologically with either needle biopsy or excision. Solid lesions that are indeterminate or suspicious on sonography should be biopsied, preferably under ultrasound guidance. If an intracystic mass is identified sonographically, surgical excision is recommended.

In interpreting the results of the biopsy, it is important to determine whether the pathologic diagnosis is concordant with the findings on CBE

and the diagnostic imaging studies. Discordant results should prompt reevaluation of the clinical examination and imaging studies as well as the pathologic diagnosis. Repeat biopsy, either ultrasound-guided needle biopsy or excisional biopsy, may be necessary. Any biopsy that yields indeterminate findings or reveals atypia may necessitate excision to ascertain the correct diagnosis.

### Asymmetric Thickening or Nodularity

An area of asymmetric thickening or nodularity is less distinct than a dominant mass, and for many health care providers it carries a slightly less ominous connotation. All cases of asymmetric thickening or nodularity should be assessed with sonography. Mammography is considered a necessary part of the diagnostic evaluation only for women 30 years of age or older. Women under the age of 30 years should have mammography only if it is clinically indicated—e.g., in the case of abnormal findings on sonography.

If the findings on mammography and sonography are negative, additional diagnostic evaluation can be limited to a follow-up CBE in 3–6 months to assess stability. In the case of stable findings on CBE, the patient can return to routine screening; in the case of progression of the area of thickening or nodularity, the lesion would most appropriately be further evaluated according to the guidelines for evaluation of a dominant mass.

Women with abnormal mammographic findings (BI-RADS category 3, 4, or 5) should undergo diagnostic evaluation as previously described (in the section "Mammographic Abnormality with Normal Findings on CBE").

### Nipple Discharge

It is important to characterize nipple discharge so that an appropriate diagnostic evaluation can be conducted. Discharge that is nonspontaneous and from multiple ducts should not raise suspicion of breast cancer. For women aged 40 years or older, diagnostic mammography should be done as would be recommended for any woman in this age group. Women with mammographic findings classified as BI-RADS category 0, 3, 4, or 5 should be cared for according to the guidelines for evaluation of mammographic abnormalities with normal findings on CBE. Women with this type of nipple discharge should be instructed to stop compression of the breast and elicitation of the nipple discharge. They should also be advised to report if the discharge becomes spontaneous.

The most worrisome discharge is spontaneous, unilateral discharge from a single duct, typically serous, sanguinous, or serosanguinous in nature. A diagnostic mammogram is the initial step in the diagnostic evaluation of this type of discharge. Lesions classified as BI-RADS category 4 or 5 should be evaluated according to the guidelines for evaluation of mammographic abnormalities with normal findings on CBE.

Unless breast conservation therapy is planned, a diagnosis of cancer in the breast under evaluation will usually end the diagnostic evaluation. If breast conservation therapy is planned, no malignancy is diagnosed, or the mammographic findings are classified as BI-RADS category 1, 2, or 3, then ductography should be performed as the prelude to a duct excision. Duct excision not only allows a pathologic diagnosis of the etiology of the nipple discharge but also allows for resolution of the discharge. Although nipple discharge is rarely a symptom of cancer, it is important to rule this out as well as to manage the patient's symptoms.

### Skin Changes

Although seemingly innocuous, skin changes of the breast require careful evaluation. Not uncommonly, patients are seen in the Cancer Prevention Center for evaluation of an isolated skin change of the breast that turns out to be a symptom of breast cancer. These patients have frequently been reassured by their outside health care provider that the skin findings are of no consequence. Special attention should be given to any breast skin change in a woman over the age of 40 years. The primary considerations are inflammatory breast cancer—with the usual skin changes of erythema and peau d'orange (skin thickening)—and Paget's disease, symptoms of which can include scaling, eczema, or nipple excoriation. Mammographic and/or sonographic evaluation is undertaken as indicated by age and other breast findings. Abnormalities found on diagnostic imaging should be evaluated according to the guidelines for evaluation of mammographic abnormalities with normal findings on CBE. If inflammatory breast cancer is a consideration and mammographic findings are benign, further evaluation with a skin punch biopsy or blind core needle biopsy of breast parenchyma is warranted. Benign findings on biopsy should prompt reassessment and possible rebiopsy, depending on the level of suspicion.

## Conclusion

The paradigm for breast cancer prevention has changed dramatically in the past decade. Whereas the focus was once on breast cancer screening, now the paradigm has expanded to include breast cancer risk assessment and primary prevention strategies. Women who present for breast cancer screening should have a risk assessment performed and be counseled regarding risk reduction options. Breast cancer prevention and screening recommendations should be risk based.

Any clinical or mammographic breast abnormality should be subjected to diagnostic evaluation. A key component of this evaluation is concordance between the results of diagnostic evaluation and the initial clinical findings and level of suspicion. Discordant results should prompt reevaluation.

## KEY PRACTICE POINTS

- Unless a genetic predisposition is suspected, the initial step of breast cancer prevention is risk assessment using the NCI Breast Cancer Risk Assessment Tool.
- Risk-based breast cancer screening recommendations should be reinforced regardless of the level of breast cancer risk.
- Women at increased risk for breast cancer should receive information and counseling about risk reduction options and the risks and benefits of risk reduction therapy.
- Clinical and mammographic breast abnormalities can be systematically evaluated. In the diagnostic work-up, concordance between the final diagnostic imaging and pathologic results and the initial clinical findings and level of suspicion is essential.

The mission of M. D. Anderson's Cancer Prevention Center is to provide research-based cancer risk assessment and risk reduction counseling as well as primary and secondary cancer prevention services for individuals with a cancer concern. Women with average or increased risk of breast cancer can be referred by their outside physician or can self-refer to any of the programs offered.

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