

524 activity may be inactivated in sporadic cases of human breast cancer. Finally, increased expression of a dominant oncogene plays a role in about a quarter of human breast cancer cases. The product of this gene, a member of the epidermal growth factor receptor superfamily, is called *erbB2* (HER/2 neu) and is overexpressed in these breast cancers due to gene amplification; this overexpression can contribute to transformation of human breast epithelium and is the target of effective systemic therapy in adjuvant and metastatic disease settings. A series of acquired “driver” mutations have been identified in sporadic breast cancer by major sequencing consortia. Unfortunately, most occur in no more than 5% of cases and generally do not have effective agents to target them, so “personalized medicine” is for now more of a dream than a reality.

## EPIDEMIOLOGY

Breast cancer is a hormone-dependent disease. Women without functioning ovaries who never receive estrogen replacement therapy do not develop breast cancer. The female-to-male ratio is about 150:1. For most epithelial malignancies, a log-log plot of incidence versus age shows a single-component straight-line increase with every year of life. A similar plot for breast cancer shows two components: a straight-line increase with age but with a decrease in slope beginning at the age of menopause. The three dates in a woman’s life that have a major impact on breast cancer incidence are age at menarche, age at first full-term pregnancy, and age at menopause. Women who experience menarche at age 16 years have only 50–60% of the breast cancer risk of a woman having menarche at age 12 years; the lower risk persists throughout life. Similarly, menopause occurring 10 years before the median age of menopause (52 years), whether natural or surgically induced, reduces lifetime breast cancer risk by about 35%. Women who have a first full-term pregnancy by age 18 years have a 30–40% lower risk of breast cancer compared with nulliparous women. Thus, length of menstrual life—particularly the fraction occurring before first full-term pregnancy—is a substantial component of the total risk of breast cancer. These three factors (menarche, age of first full-term pregnancy, and menopause) can account for 70–80% of the variation in breast cancer frequency in different countries. Also, duration of maternal nursing correlates with substantial risk reduction independent of either parity or age at first full-term pregnancy.

International variation in incidence has provided some of the most important clues on hormonal carcinogenesis. A woman living to age 80 years in North America has one chance in nine of developing invasive breast cancer. Asian women have one-fifth to one-tenth the risk of breast cancer of women in North America or Western Europe. Asian women have substantially lower concentrations of estrogens and progesterone. These differences cannot be explained on a genetic basis because Asian women living in a Western environment have sex steroid hormone concentrations and risks identical to those of their Western counterparts. These migrant women, and more notably their daughters, also differ markedly in height and weight from Asian women in Asia; height and weight are critical regulators of age of menarche and have substantial effects on plasma concentrations of estrogens.

The role of diet in breast cancer etiology is controversial. While there are associative links between total caloric and fat intake and breast cancer risk, the exact role of fat in the diet is unproven. Increased caloric intake contributes to breast cancer risk in multiple ways: earlier menarche, later age at menopause, and increased postmenopausal estrogen concentrations reflecting enhanced aromatase activities in fatty tissues. On the other hand, central obesity is both a risk factor for occurrence and recurrence of breast cancer. Moderate alcohol intake also increases the risk by an unknown mechanism. Folic acid supplementation appears to modify risk in women who use alcohol but is not additionally protective in abstainers. Recommendations favoring abstinence from alcohol must be weighed against other social pressures and the possible cardioprotective effect of moderate alcohol intake. Chronic low-dose aspirin use is associated with a decreased incidence of breast cancer. Depression is also associated with both occurrence and recurrence of breast cancer.

Understanding the potential role of exogenous hormones in breast cancer is of extraordinary importance because millions of American women regularly use oral contraceptives and postmenopausal hormone replacement therapy. The most credible meta-analyses of oral contraceptive use suggest that these agents cause a small increased risk of breast cancer. By contrast, oral contraceptives offer a substantial protective effect against ovarian epithelial tumors and endometrial cancers. Hormone replacement therapy (HRT) has a powerful effect on breast cancer risk. Data from the Women’s Health Initiative (WHI) trial showed that conjugated equine estrogens plus progestins increased the risk of breast cancer and adverse cardiovascular events but decreased the risk of bone fractures and colorectal cancer. On balance, there were more negative events with HRT; 6–7 years of HRT nearly doubled the risk of breast cancer. A parallel WHI trial with >12,000 women enrolled testing conjugated estrogens alone (estrogen replacement therapy in women who have had hysterectomies) showed no significant increase in breast cancer incidence. Thus, there are serious concerns about long-term HRT use in terms of cardiovascular disease and breast cancer. The WHI trial of conjugated equine estrogen alone demonstrated few adverse effects for women age <70; however, no comparable safety data are available for other more potent forms of estrogen replacement, and they should not be routinely used as substitutes. HRT in women previously diagnosed with breast cancer increases recurrence rates. Rapid decrease in the number of women on HRT has already led to a coincident decrease in breast cancer incidence.

In addition to the other factors, radiation is a risk factor in younger women. Women who have been exposed before age 30 years to radiation in the form of multiple fluoroscopies (200–300 cGy) or treatment for Hodgkin’s disease (>3600 cGy) have a substantial increase in risk of breast cancer, whereas radiation exposure after age 30 years appears to have a minimal carcinogenic effect on the breast.

## EVALUATION OF BREAST MASSES IN MEN AND WOMEN

Because the breasts are a common site of potentially fatal malignancy in women, examination of the breast is an essential part of the physical examination. Unfortunately, internists frequently do not examine breasts in men, and in women, they are apt to defer this evaluation to gynecologists. Because of the plausible association between early detection and improved outcome, it is the duty of every physician to identify breast abnormalities at the earliest possible stage and to institute a diagnostic workup. Women should be trained in breast self-examination (BSE). Although breast cancer in men is unusual, unilateral lesions should be evaluated in the same manner as in women, with the recognition that gynecomastia in men can sometimes begin unilaterally and is often asymmetric.

Virtually all breast cancer is diagnosed by biopsy of a nodule detected either on a mammogram or by palpation. Algorithms have been developed to enhance the likelihood of diagnosing breast cancer and reduce the frequency of unnecessary biopsy (Fig. 108-1).

### THE PALPABLE BREAST MASS

Women should be strongly encouraged to examine their breasts monthly. A potentially flawed study from China has suggested that BSE does not alter survival, but given its safety, the procedure should still be encouraged. At worst, this practice increases the likelihood of detecting a mass at a smaller size when it can be treated with more limited surgery. Breast examination by the physician should be performed in good light so as to see retractions and other skin changes. The nipple and areolae should be inspected, and an attempt should be made to elicit nipple discharge. All regional lymph node groups should be examined, and any lesions should be measured. Physical examination alone cannot exclude malignancy. Lesions with certain features are more likely to be cancerous (hard, irregular, tethered or fixed, or painless lesions). A negative mammogram in the presence of a persistent lump in the breast does not exclude malignancy. Palpable lesions require additional diagnostic procedures, including biopsy.

In premenopausal women, lesions that are either equivocal or nonsuspicious on physical examination should be reexamined in 2–4