

CHAPTER

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Breast Cancer

- Breast cancer is the most frequently diagnosed cancer among women.
- In 2000, an estimated 182,800 women in the United States will be newly diagnosed with breast cancer, and an estimated 40,800 women will die of the disease.
- Breast cancer incidence and mortality patterns vary substantially among the major ethnic groups.
- There has been a trend over time toward diagnosis of smaller size tumors for all ethnic groups, probably due to early mammographic screening.

Breast Cancer in the United States

Breast cancer is the most common type of cancer in women and the second leading cause of cancer-related deaths. In 2000, the American Cancer Society (ACS) estimates that approximately 182,800 new cases of invasive breast cancer will be diagnosed and that 40,800 women will die from this disease. Approximately one out of every eight women in the United States who lives to be 85 years or older will develop breast cancer during her lifetime.

However, women have a good chance of surviving breast cancer for many years when it is detected early. Nationwide, the 5-year relative survival rate for women diagnosed with *in situ* breast cancer is 97%, up from 78% in the 1940s. Early detection is essential in effective treatment of breast cancer: the 5-year survival rate drops to 78% for cancer diagnosed at a regional stage and as low as 22% for cancer diagnosed at a distant stage (ACS, 2000).

About 0.9% of breast cancer in the United States affects males. In 2000, 1400 new cases of breast cancer are expected to be diagnosed in men. Notable differences from women include older age at presentation and subareolar location. Diagnosis at advanced stages, rather than indicating a more aggressive disease than in women, is often a result of inattention and delay of diagnosis.

Incidence—Nationwide Trends: Breast cancer incidence increased more or less steadily between 1940 and 1987 and has since stabilized at 109.6 cases per 100,000 women. Non-Hispanic white women are more likely to develop breast cancer than African American women (or other ethnic groups such as Hispanic or American Indian women). Incidence rates increased more for older women than younger, and more for African American than for non-Hispanic white women. **This increase and later stabilization of rates is believed to be related to increased use of breast cancer screening methods, particularly mammography.**

Since the major risk factors for developing breast cancer (such as age, gender, and genetic susceptibility to cancer) are inherited or otherwise beyond women's control, identifying and addressing factors which can lead to prevention and early stage diagnosis of breast cancer are essential to improving breast cancer survival and women's health. Nationally, women over age 50, women who have low formal education levels, women of low socioeconomic status, and African American women are at particular risk for later stage breast cancer at diagnosis and have lower overall survival rates.

Mortality—Nationwide Trends: Mortality from breast cancer has been relatively stable since 1950 but since 1989 has declined 5.5% among non-Hispanic white women nationwide. However, mortality increased 2.6% for African American women during the same period. The recent decline in breast cancer mortality among non-Hispanic white women has been attributed in part to increases in breast cancer awareness and screening, leading to increased diagnosis of the disease at earlier stages (ACS, 2000).

Probability of Developing Invasive Breast Cancer Over Selected Age Intervals, United States, 1994–1996

Probability

Birth to 39 years	1 in 235
40 to 59 years	1 in 25
60 to 79 years	1 in 15
Birth to Death	1 in 8

American Cancer Society, Surveillance Research

Risk Factors for the Development of Breast Cancer

Lifetime risk is the probability that an individual, over the course of a lifetime, will be diagnosed with or die from cancer. A woman in the United States has a 12.6%, or 1 in 8 risk of developing breast cancer, and a 3.6%, or 1 in 28 risk of dying from breast cancer over her lifetime.

Relative risk is a measure of the strength of the relationship between risk factors and cancer. Cancer risk factors can either be conditions which directly cause the disease (e.g., smoking and lung cancer) or personal characteristics which are only indirectly associated with cause — as is the case for almost all the risk factors for breast cancer.

Established Risk Factors for Breast Cancer:

Sex: Breast cancer is overwhelmingly a disease of women.

Increasing Age: Breast cancer risk increases dramatically after age 45. Risk declines for women age 80 and older.

Personal History of Breast Cancer: Invasive and *in situ* breast cancers increase the lifetime risk of developing a new breast cancer in any remaining breast tissue in either breast. Women whose first breast cancer was diagnosed before age 50 are at greatest risk of having a second primary breast cancer. A contralateral primary breast cancer occurs in approximately 15% of these women.

Family History of Breast Cancer: Any family history of breast cancer is associated with an increase in risk. However, only a history of breast cancer in a first-degree relative (mother, sister, or daughter), particularly a breast cancer diagnosed before menopause, is associated with a significant increase. Most family history of breast cancer probably does not represent a direct genetic inheritance link but rather life-style similarities and the inheritance of selected risk factors (menstrual patterns, obesity). Most genetically determined breast cancers occur at

Primary Risk Factors for Developing Breast Cancer

- Sex (being female)
- Increasing age
- Personal history of breast cancer
- Family history of breast cancer
- Personal history of benign breast disease

younger ages, are more likely to be bilateral, and appear in multiple family members over three or more generations.

Personal History of Benign Breast Disease: Biopsy-confirmed benign breast disease is associated with an increased risk of breast cancer. This risk may be confined primarily to women with diagnoses of atypical (lobular or ductal) hyperplasia.

Other Risk Factors

Hormonal Factors: Increased lifetime exposure to female hormones may increase a woman's lifetime risk of developing breast cancer. Situations which can increase this exposure include:

- Early age at menarche
- Late age at menopause
- Late age at first live birth
- Few pregnancies/low parity
- Hormone therapy

Hormone Therapy: Endogenous estrogens are the principal regulator of growth and differentiation in normal breast tissue during puberty and pregnancy. There is substantial epidemiological and experimental evidence that hormones are also important in the etiology of breast cancer. Risks associated with the use of oral contraceptives (OC) are not well defined, though a recent meta-analysis found that current users of OCs had a higher relative risk of breast cancer (RR 1.24) than women who had never used oral contraceptives. Notably, tumors diagnosed in women who were using or had used OCs were generally less advanced clinically than those diagnosed in women who had never used OCs. (Collaborative group, 1996).

Use of hormone replacement therapy (HRT) is associated with an increased risk of invasive breast cancer. Women currently receiving HRT for menopause have an increased breast cancer risk (RR 1.36) and this risk may rise in women who use HRT beyond five years. Nevertheless, HRT has been speculated to improve cardiovascular measures and prevent bone loss, along with relieving menopausal symptoms (Colditz, 1995). More recent studies have shown that HRT with estrogen and progestin appears to increase the risk of breast cancer compared to the use of estrogen alone. Some researchers speculate progestin's adverse impact on breast tissue may make sense since cell division in the breast is greatest during the part of

the menstrual cycle when the most progesterone is produced (Ross, 2000; Schairer, 2000). Because of the studies' designs, caution should be used in interpreting these results. However, these studies suggest that postmenopausal estrogen use for more than 5–10 years increases a woman's risk for breast cancer, and that the addition of progestin increases that risk further. The decision to use HRT should include an assessment of the risks and benefits in each individual.

Radiation Exposure: Excessive exposure to ionizing radiation may increase risk since breast tissue appears to be particularly sensitive to the carcinogenic action of radiation.

History of Other Cancers: History of endometrial, ovarian, and/or colon cancer increases lifetime risk for breast cancer.

BRCA1/2 Carriers: Both prospective and retrospective genetic epidemiologic studies have demonstrated that women who carry mutations in either BRCA1 or BRCA2 genes are at very high risk for developing both breast (50–85%) and ovarian (10–45%) cancers (Thorlacijs, 1998). It is not known whether anti-estrogens, or any chemoprevention drug, can prevent the development of malignancy in women with heritable risk. It does appear that both BRCA 1 and 2 act in part as tumor suppressor genes. Women with genetic mutations may appear to be candidates for tamoxifen, but there is no data yet available that relates directly to them (Vogel, 2000). Until these studies are completed, the use of these anti-estrogenic agents in women with BRCA 1 and BRCA 2 carriers should be limited to the research setting.

Obesity/Dietary Fat Intake: Some researchers hypothesize that high fat intake may increase breast cancer risk. The major evidence behind this hypothesis is that per capita fat consumption around the world is highly correlated with national breast cancer mortality (Lipworth, 1994). Collectively, the evidence from case-control studies suggests that fat intake during adult life may be associated with a modest increase in the risk of breast cancer (Lipworth, 1994), and a greater incidence of breast cancer occurs in postmenopausal women who are obese. However, there are many potential limitations to these studies and no definitive results. The cohort studies have found no link between breast cancer and dietary fat (Hunter, 1996).

Socioeconomic Status: Breast cancer is more common in women of higher socioeconomic status. This increased risk may be due to early menarche (which may or may not be related to socioeconomic status), late age for first birth, and low parity. Women with higher formal education, for example, are likely to have their first child later and to have fewer children. In addition, availability and accessibility of screening methods and health care may contribute to a higher incidence of reporting for this group.

Alcohol, Pesticides, Diet, Smoking, and Lack of Exercise have also been investigated as possible risk factors for breast cancer, but causal relationships have not been established. Increased folate intake may be protective against breast cancer (Zhang, 1999).

Chemoprevention

Tamoxifen: Tamoxifen has historically been used to treat rather than prevent breast cancer. Several breast cancer treatment trials reported a decrease in the incidence of contralateral breast cancers. The National Surgical Adjuvant Breast and Bowel Project (NSABP) designed a study, the Breast Cancer Prevention Trial, to assess the efficacy of tamoxifen for breast cancer prevention in women at increased risk for the disease. The relative risk was reduced by 44% in women 49 years or younger, 51% in women 50-59 years and 55% in women 60 years and older. Endometrial cancers were more common in those using tamoxifen and the rates of stroke (RR 1.59), pulmonary embolism (RR 3.01) and deep venous thrombosis (RR 1.60) were elevated as well in the tamoxifen group. Tamoxifen is approved in the US for reduction of breast cancer risk in women at high risk for the disease, based on the NSABP trial. Only women at increased risk should consider tamoxifen and they should receive therapy for five years (Vogel, 2000).

Raloxifene: Raloxifene acts on reproductive hormones and is being examined for breast cancer risk reduction. The Study of Tamoxifen and Raloxifin (STAR) trial is currently enrolling participants. This trial tests the risk reduction for tamoxifen and raloxifene in a randomized, controlled manner with breast cancer incidence as the primary end point.

Other anti-estrogens, i.e., toremifene citrate and droloxifene, may also be useful in preventing breast cancer. Another approach to breast cancer prevention is the use of retinoids. However, no large-scale studies of the use of these compounds for prevention have been completed as of yet.

