

Hispanic women, and 46 for African American women. Only 20% of non-Hispanic white women are diagnosed at ages younger than 50 years, compared with 35% of African American women and 31% of Hispanic women. The incidence of ER-negative and HER2-positive cancers is relatively constant in all ethnic groups, but the number of ER-positive cancers is lower in non-white women.

The risk of death from breast cancer in those diagnosed with the disease remained constant for many years, but since 1994 has gradually declined from 30% to about 20%. This decrease is attributed to mammographic screening as well as more effective treatment modalities. However, the decline in the death rate has been less impressive for African American women, who have the highest mortality rate (Fig. 23-15). Although this difference is explained partly by unequal access to care, breast cancers in African American women are also on average more biologically aggressive, as they are more likely to be ER-negative and to have a high nuclear grade.

The incidence of breast cancer is four to seven times higher in the United States and Europe than in other countries, but rates are rising worldwide and by 2020 it is estimated that 70% of cases will be in developing countries. This change in incidence likely stems from adoption of Western social lifestyles, including delayed pregnancy, fewer pregnancies, and decreased breastfeeding.

**Risk Factors.** Beyond female sex (99% of those affected are female), the major risk factors are related to hereditary factors, lifetime exposure to estrogen and, to a lesser extent, environmental or lifestyle factors. Among the large number of identified risk factors are the following:

- **Germline mutations.** Approximately 5% to 10% of breast cancers occur in persons with germline mutations in tumor suppressor genes (discussed later). For these individuals, the lifetime risk of breast cancer can be more than 90%.
- **First-degree relatives with breast cancer.** About 15% to 20% of women with breast cancer have an affected first-degree relative (mother, sister, or daughter), but do not carry an identified breast cancer gene mutation. This increased risk is probably due to the interaction of low-risk susceptibility genes and shared environmental factors. Genome-wide association studies are being used to identify candidate genetic variants. It is important to note that risk is not increased if the only affected relative is a postmenopausal mother with cancer.
- **Race/ethnicity.** Ethnic background is correlated with breast cancer risk. Non-Hispanic white women have the highest incidence in the United States (Fig. 23-15). Variation in the frequency of breast cancer genes across ethnic groups is partly responsible for these differences. For example, germline *BRCA1* and *BRCA2* mutations are particularly prevalent in Ashkenazi Jewish populations.
- **Age.** Breast cancer risk rises throughout a woman's lifetime, peaking at 70 to 80 years and then declining slightly thereafter (Fig. 23-13).
- **Age at menarche.** Menarche at ages younger than 11 years increases risk by 20% compared to menarche at ages greater than 14. Late menopause also increases risk.
- **Age at first live birth.** A full-term pregnancy before the age of 20 halves the risk compared to nulliparous women or women who are older than the age of 35 at the time of their first birth.
- **Benign breast disease.** A prior breast biopsy revealing atypical hyperplasia or proliferative changes increases the risk of invasive carcinoma (Table 23-1).
- **Estrogen exposure.** Menopausal hormone therapy increases the risk of breast cancer, particularly when estrogen and a progestin are given together for a period of years. Most excess cancers are small ER-positive carcinomas. In contrast, oral contraceptives do not appear to increase the risk of breast cancer. Reducing endogenous estrogens by oophorectomy decreases the risk of developing breast cancer by up to 75%. Drugs that block estrogenic effects (e.g., tamoxifen) or block the formation of estrogen (e.g., aromatase inhibitors) also decrease the risk of ER-positive breast cancer.
- **Breast density.** Women with very dense breasts on mammography have a four- to six-fold higher risk of both ER-positive and ER-negative breast cancer compared to women with the lowest density. High breast density clusters in families and is correlated with other risk factors such as older age at first birth, fewer children, and menopausal hormone therapy. Persistently high breast density in older women may stem from a failure of normal breast involution.
- **Radiation exposure.** Radiation to the chest, whether for cancer therapy, due to atomic bomb exposure, or nuclear accidents, results in a higher rate of breast cancer. The risk is greatest with exposure at young ages and with high radiation doses. For example, women in their teens and early 20s who received radiation to the chest for Hodgkin lymphoma have a 20% to 30% risk of developing breast cancer over 10 to 30 years. Older women undergoing radiation do not incur this risk.
- **Carcinoma of the contralateral breast or endometrium.** Approximately 1% of women with breast cancer develop a second contralateral breast carcinoma per year. Breast and endometrial carcinomas have several risk factors in common, the most important of which is exposure to prolonged estrogenic stimulation.
- **Diet.** Large studies have failed to find strong correlations between breast cancer risk and dietary intake of any specific type of food. Moderate or heavy alcohol consumption increases risk.
- **Obesity.** Obese women under the age of 40 have a decreased risk as a result of anovulatory cycles and lower progesterone levels. In contrast, postmenopausal obese women are at an increased risk, which is attributed to the synthesis of estrogens in fat depots.
- **Exercise.** There is a probable small protective effect for women who are physically active.
- **Breastfeeding.** The longer women breastfeed, the greater the reduction in risk. Lactation suppresses ovulation and may trigger terminal differentiation of luminal cells. The lower incidence of breast cancer in developing countries can largely be explained by the more frequent and longer nursing of infants.
- **Environmental toxins.** There is concern that environmental contaminants, such as organochlorine pesticides, have estrogenic effects on humans. Possible links to