Chapter 2
Epidemiology of Breast Cancer in Women

Steven S. Coughlin and Yasmin Cypel

Abstract Epidemiologic studies have contributed importantly to current knowledge of environmental and genetic risk factors for breast cancer. Worldwide, breast cancer is an important cause of human suffering and premature mortality among women. In the United States, breast cancer accounts for more cancer deaths in women than any site other than lung cancer. A variety of risk factors for breast cancer have been well-established by epidemiologic studies including race, ethnicity, family history of cancer, and genetic traits, as well as modifiable exposures such as increased alcohol consumption, physical inactivity, exogenous hormones, and certain female reproductive factors. Younger age at menarche, parity, and older age at first full-term pregnancy may influence breast cancer risk through long-term effects on sex hormone levels or by other biological mechanisms. Recent studies have suggested that triple negative breast cancers may have a distinct etiology. Genetic variants and mutations in genes that code for proteins having a role in DNA repair pathways and the homologous recombination of DNA double stranded breaks (BRCA1, BRCA2, XRCC2, XRCC3, ATM, CHEK2, PALB2, RAD51), have been implicated in some cases of breast cancer.

Keywords Incidence · International trends · Risk factors · Anthropometric factors · Mammographic breast density · Ionizing radiation exposure · Environmental exposures · Genetic factors · Gene mutations · Genetic polymorphisms · Family history · Race
2.1 Introduction

The global burden of breast cancer in women, measured by incidence or mortality, is substantial and rising in several countries [1, 2]. Breast cancer is the most commonly diagnosed invasive cancer in the United States for women of all racial and ethnic groups, with an estimated 230,480 new cases diagnosed in 2011 [3]. Breast cancer accounts for more cancer deaths among United States women than any site other than lung cancer. Breast cancer also occurs in men [4], but the disease is rare among men and there is a pronounced female-to-male disparity in breast cancer incidence. This chapter provides a summary of the distribution and determinants of breast cancer in women including both the descriptive epidemiology of the disease and an up-to-date review of risk factors identified in epidemiologic studies.

2.1.1 Incidence and Mortality Rates in the US

Breast cancer incidence and death rates increase with age; about 95% of new cases occur in women 40 years of age and older [3]. Breast cancer incidence rates in the United States continue to rise after menopause and are highest in the older age categories. Age-standardized incidence rates are higher among white women than black women, although black women in the United States have a higher mortality rate than white women. Incidence rates for Asian/Pacific Islander, American Indian/Alaska Native, and Hispanic women in the United States are generally lower than those for white or black women [5, 6] (Fig. 2.1).

The incidence of breast cancer in the United States increased until about 2000 then decreased from 2002 to 2003 [7]. Most of the decrease in that period was among women with estrogen receptor positive cancers [8].

2.1.2 International Trends in Breast Cancer Incidence and Mortality

Worldwide, an estimated 1.4 million women were diagnosed with breast cancer in 2008 and about 458,400 women died from the disease that same year [2]. Breast cancer incidence rates tend to be higher among more affluent women, both within countries and internationally (Fig. 2.2). More than two-thirds of breast cancer cases are diagnosed in women aged 50 years and older; the majority of these cases are in developed countries [9]. For women aged 15–49 years, twice as many breast cancer cases are diagnosed in developing countries than in developed countries [9]. Between 1980 and the late 1990s, breast cancer incidence rates rose about 30% in westernized countries [2]. This trend was likely due to changes in
reproductive patterns and increased screening. In the last decade, breast cancer incidence rates rose in many Asian and African countries [2]. In countries where mammography is available or affordable, adherence to recommendations for routine screening is associated with reduced mortality from breast cancer. Over the past two decades, breast cancer mortality has been stable or decreasing in many countries in Europe and North America [2].
2.2 Risk Factors

A variety of risk factors for breast cancer have been well-established by epidemiologic studies carried out to date, in addition to increasing age and female sex. These risk factors include nonmodifiable factors such as race, ethnicity, and genetics, as well as modifiable exposures related to diet, physical inactivity, exogenous hormones, and certain female reproductive factors. Circulating levels of endogenous sex steroid hormones such as estradiol have been associated with increased risk of breast cancer among postmenopausal women [10]. Sex hormone levels are strongly associated with some risk factors for breast cancer (for example, obesity and higher alcohol consumption) and may mediate the effects of these factors on breast cancer risk [11].

2.2.1 Race

Several factors may account for racial differences in breast cancer mortality including socioeconomic factors, access to screening mammography and timely treatment, and biological factors. In the United States, Hispanic ethnicity and black race have been associated with later stage at breast cancer diagnosis [12]. Compared with white women in the United States, black women tend to have more aggressive breast cancers that present more frequently as estrogen receptor negative tumors [13]. Among premenopausal women, tumors that are estrogen receptor negative, progesterone receptor negative, and HER2 negative (“triple negative” tumors) are more common among black women than among white women.

2.2.2 Age at Menarche, Parity, and Age at First Live Birth

Younger age at menarche, parity, and older age at first full-term pregnancy are well-established risk factors for breast cancer. These risk factors may influence breast cancer risk through long-term effects on sex hormone levels in premenopausal women, through long-lasting changes in breast tissue, or by other biological mechanisms [14]. Reproductive hormones may influence breast cancer risk by increasing cell proliferation and increasing the likelihood of damage to DNA or by promoting cancer growth [3]. In a pooled analysis of control group data from 13 studies of postmenopausal women, circulating levels of estradiol were 6% lower in women who had menarche at ages 14 years or older than in women who had menarche before 12 years [11].

Nulliparity increases breast cancer risk in older women [15]. Results from a cohort study of Norwegian women indicated that nulliparity and obesity may have a synergistic effect on breast cancer risk among older women [16]. In the Black
Women’s Health Study in the United States [17], higher parity was associated with a reduced risk of estrogen receptor positive/progesterone receptor positive breast cancer (hazard ratio $= 0.53$, 95% CI $0.39$–$0.73$ for $3 +$ versus $0$ births, $p(\text{trend}) = 0.0002$). Pregnancy may reduce breast cancer risk by bringing about persistent changes in the mammary gland that make the breast less susceptible to carcinogenic factors [16]. Younger age at first live birth is protective.

### 2.2.3 Breast Feeding

Breast feeding reduces a woman’s risk of breast cancer and is an important modifiable preventive behavior. Longer duration of breast feeding has been associated with a greater reduction in breast cancer risk. The higher incidence of estrogen receptor negative/progesterone receptor negative breast cancer among black women in the United States may be partly explained by their lower prevalence of breastfeeding relative to white women [17].

### 2.2.4 Menopausal Status and Age at Menopause

Older age at menopause is also a well-recognized risk factor for breast cancer. Both early menarche and older age at menopause increase lifetime exposure of breast tissue to hormones. Menopause hormone therapy is discussed below in Sect. 2.4.6.

### 2.2.5 Oral Contraceptives

Epidemiologic studies of oral contraceptive use and breast cancer risk have generally shown little or no increased risk [18]. Recent use of oral contraceptives may slightly increase the risk of breast cancer [3]. In an analysis of data from a multicenter, population-based case–control study, Marchbanks et al. found that breast cancer risk did not vary by oral contraceptive formation [18]. No formulation was significantly associated with an increased risk of breast cancer.

### 2.2.6 Hormone Therapy

Results from observational studies and the Women’s Health Initiative Randomized Trial indicate that hormone replacement therapy after menopause increases breast cancer risk [19–21]. Use of a regimen that includes both estrogen and progesterone has been associated with a higher risk of breast cancer than the use of estrogen
alone [19]. Studies of breast cancer incidence in the United States, Canada, and European countries showed a 5–10% decline in breast cancer incidence following reductions in hormone therapy (HT) use after 2002 [22]. In several countries, however, temporal changes in screening mammography are also likely to have played a role in the decline in breast cancer incidence. Women who do not currently use HT may also undergo screening mammography less frequently [22, 23].

### 2.2.7 Diet

A wide variety of dietary factors have been examined as potential breast cancer risk factors in case–control and prospective studies, including increased consumption of alcohol [24–26], red meat, processed meat, and animal fat, and decreased consumption of fruits and vegetables, calcium, vitamin D, soy, and antioxidants such as beta-carotene and other carotenoids, vitamin C, and vitamin E [27, 28]. The ratio of omega-3 to omega-6 fatty acids has also been examined in relation to breast cancer risk. Although initial studies suggest that a higher ratio of omega-3 to omega-6 fats may reduce breast cancer risk, more research is warranted [29]. For most dietary factors, epidemiologic studies of breast cancer have provided inconsistent or inconclusive results. A notable exception is alcohol consumption, which is discussed separately below.

Foods with a high glycemic index and glycemic load and dietary carbohydrates, which can influence blood glucose and insulin concentrations, have also been examined in relation to breast cancer risk [30–33]. The glycemic index is an indicator of the blood sugar response of the body to a standardized amount of carbohydrate in food. The glycemic load takes into account the amount of food consumed [29]. A meta-analysis by Mulholland et al., which focused on cohort study results, showed no overall association between postmenopausal breast cancer risk and glycemic load intake (RR = 1.03, 95% CI 0.94–1.12) [34].

In a recent meta-analysis of prospective studies (14 studies of breast cancer incidence and 4 studies of breast cancer recurrence), Dong and Qin found that soy isoflavones consumption was inversely associated with breast cancer risk (RR = 0.89, 95% CI 0.79–0.99). However, the protective effect of soy was only observed among studies conducted in Asian populations [27].

### 2.2.8 Alcohol

An increasing number of epidemiologic studies have implicated alcohol consumption as a risk factor for breast cancer [24–26]. Studies have shown a linear dose–response relation between alcohol consumption and breast cancer risk. Chen et al. examined the association of breast cancer with alcohol consumption among 105,986 women enrolled in the Nurses’ Health Study, of whom 7,690 developed
invasive breast cancer over the period 1980 through June 2008. Alcohol consumption was significantly associated with increased breast cancer risk even at levels as low as 5.0–9.9 g per day, or about 3–6 drinks per week (RR = 1.15, 95% CI 1.06–1.24). Cumulative average alcohol consumption over long periods of time was found to be the most relevant measure [24]. The possible biological mechanisms include alcohol’s effects on circulating estrogen levels.

2.2.9 Physical Activity

There is considerable evidence from epidemiologic studies that high levels of physical activity reduces breast cancer risk in women. The possible biological mechanisms include the influences of physical activity on body composition, insulin resistance, and circulating levels of sex steroid hormones [35]. In the Women’s Health Initiative Cohort Study, which involved 74,171 women aged 50–79 years recruited by 40 United States clinical centers, women who engaged in regular strenuous physical activity at age 35 had a 14% decreased risk of breast cancer (RR = 0.86, 95% CI 0.78–0.95) compared to inactive women [36]. Similar but attenuated findings were observed for strenuous physical activity at ages 18 years and 50 years. The study results also indicated that longer duration of physical activity provides the most benefit [36].

2.2.10 Anthropometric Factors

Anthropometric factors such as body height, weight, and adiposity have been extensively studied in epidemiologic studies of breast cancer [37, 38]. Body fat provides a substrate for the production of estrogen from androgen in adipose tissue [39]. In the Cancer Prevention Study II cohort (n = 495,477 women), Calle et al. found that women with higher values of body mass index had an increased risk of dying from breast cancer and certain other cancers [40]. Although overweight and obesity are important modifiable risk factors for breast cancer among postmenopausal women, epidemiologic studies have shown that high body mass index and other measures of adiposity are associated with a reduced risk of breast cancer among premenopausal women [41, 42]. The age at which body mass or adiposity is assessed (childhood, adolescence, or adulthood) is important. In some studies, body mass index at age 18 years and body fatness during youth have been inversely associated with breast cancer risk in both pre- and postmenopausal women [42].

Obesity and physical inactivity are important determinants of hyperinsulinemia and insulin resistance. Hyperinsulinemia with insulin resistance has been reported to be an independent risk factor for breast cancer [43].

Obesity influences the amount of free insulin-like growth factor I (IGF-I) available to cells. Breast cancer has been related to cell proliferation in response to
growth factors such as IGF-I and sex hormones [44]. Increases in serum or plasma levels of IGF-I have been observed in some epidemiologic studies of premenopausal breast cancer [45], but results to date have been inconsistent. The relationship between prediagnostic IGF-I and insulin-like growth factor binding protein-3 (IGFBP-3) levels and breast cancer risk was examined in a meta-analysis of data from 17 prospective studies conducted in 12 countries [46]. The overall odds ratio for breast cancer for women in the highest versus the lowest quintile of IGF-I concentration was 1.28 (95% CI 1.14–1.44). The positive association with IGF-I, which was not substantially modified by IGFBP-3 or menopausal status, was limited to estrogen receptor positive breast cancers.

In general, results from epidemiologic studies do not support an association between IGFBP-1 and breast cancer risk. Although results from some epidemiologic studies support an association between IGFBP-3 and risk of breast cancer among younger women, results to date have been inconsistent. Rinaldi et al. conducted a pooled analysis of data from three prospective studies in New York, Northern Sweden, and Milan, Italy [47]. Statistically nonsignificant, positive associations were observed between IGF-I and IGFBP-3 and breast cancer risk among younger women.

2.2.11 Mammographic Breast Density

Breast density is one of the strongest established risk factors for breast cancer. Women with more extensive mammographic density have over a 4-fold increased risk of breast cancer [48]. Mammographic density likely reflects the amount of epithelial and stromal cells in the breast and the proliferation of these cells but does not indicate any histological abnormality [49]. Mammographic breast density is less extensive in women who are parous and in those with a larger number of live births, and changes in response to exposure to hormones [49]. Mammographic breast density decreases throughout menopause and increases with combined hormone therapy [50]. Longitudinal epidemiologic studies have shown that mammographic density declines as women get older [51]. The change in mammographic density with age reflects a reduction in glandular tissue and increase in fat [49]. Although influenced by changes in exposure to hormones, mammographic density is also a heritable quantitative trait [50].

2.2.12 Environmental and Occupational Exposures

Exposure to ionizing radiation (as a result of nuclear explosions, diagnostic fluoroscopy, or radiotherapy in adolescence) is an established breast cancer carcinogen [52, 53]. The biological mechanism is likely to be induction of DNA mutations. The risks of breast cancer associated with a wide variety of environmental exposures
were recently reviewed by the Institute of Medicine at the request of Susan G. Komen for the Cure [54]. The IOM concluded that the evidence associating individual chemicals with breast cancer risk is not conclusive, and also recognized the need for further research in this area. The IOM noted that exposure to chemicals with estrogenic or other properties relevant to sex steroid activity, such as bisphenol A (BPA), polybrominated diphenyl ethers (PBDEs), and certain dioxins or dioxin-like compounds, may possibly influence breast cancer risk. The risk of breast cancer from exposure to 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin (TCDD) has been reviewed by several authors and expert panels with no consistent evidence of an increased risk [55]. Despite the lack of conclusive evidence from epidemiologic studies, exposures to chemicals with estrogenic or other properties relevant to sex steroid activity could influence breast cancer risk if the exposures occur at critical life stages or in combination with exposure to other similar chemicals [54].

Results from several studies support an association between shift work and disruption of the circadian rhythm with breast cancer risk. In the Nurses’ Health Study [56] a moderate increase in breast cancer risk was observed among women who worked 1–14 years (adjusted RR = 1.08, 95 % CI 0.99–1.18) or 15–29 years on rotating night shifts (adjusted RR = 1.08, 95 % CI 0.90–1.30). Levels of serum melatonin, which may have a protective effect, decrease when people are exposed to light at night. In experimental studies, the disruption of the nocturnal melatonin signal has been shown to activate human breast cancer growth, metabolism, and signaling [57].

Epigenetic changes such as DNA methylation have been associated with breast cancer in epidemiologic studies [58]. DNA methylation, which has been associated with environmental exposures such as cigarette smoke and persistent organic pollutants, may play a role in cancer causation by silencing genes through hypermethylation or, conversely, by activating genes through hypomethylation [58].

2.3 Risk Factors According to ER, PR, and HER2 Expression

As detailed in other chapters in this book, breast cancer subtypes are biologically distinct and may have distinct etiologies [59, 60]. This includes cases that express estrogen and/or progesterone receptors and those that overexpress the tyrosine kinase human epidermal growth factor receptor-2 (HER2) due to amplification of its encoding oncogene ERBB2. Using data from the Breast Cancer Surveillance Consortium (n = 743,623 women), Phipps et al. examined associations between reproductive history and breast cancer cases classified according to tumor marker expression: estrogen receptor (ER) positive (n = 8,203 cases), ER negative/progesterone receptor (PR) negative/HER2 positive (n = 288), or ER negative, PR negative, and HER2 negative (triple negative, n = 645). Nulliparity was most strongly associated with risk of ER positive breast cancer (hazard ratio = 1.31, 95 % CI 1.23–1.39). Late age at first birth was most strongly associated with risk of ER negative/PR negative/HER2 positive disease (hazard ratio = 1.83, 95 % CI
1.31–2.56). Neither parity nor age at first birth was associated with triple negative breast cancer. Studies have shown that female reproductive factors such as early age at menarche, nulliparity, and older age at first live birth are most clearly associated with hormone receptor positive tumors, suggesting that triple negative breast cancer may have a distinct etiology [61]. Recent studies, including emerging areas of research, have focused on central obesity and the metabolic syndrome as predictors of triple negative breast cancer [62].

2.4 Genetic Factors

Population-based epidemiologic studies and family-based studies have identified a number of low-penetrance genetic variants and rare, moderate-to-high penetrance genetic mutations including BRCA1 and BRCA2 gene mutations. As discussed in other chapters in this book, breast cancer is a heterogeneous disease and genetic factors likely account for pathological subtypes and much of the heterogeneity of the disease [63].

2.4.1 Family History of Cancer

Having a positive family history of breast cancer is an established risk factor for the disease. Women who have one first degree relative with breast cancer have about a two-fold increased risk of developing breast cancer [64, 65]. Risk increases the younger the relative was at the time of diagnosis and with increasing number of first-degree relatives with breast cancer [3]. About 20% of breast cancer patients have a family history of the disease in a first degree relative. Only about 5–10% of breast cancer cases associated with a family history of the disease in a first-degree relative are inherited in an autosomal dominant fashion. These cases have features such as bilaterality, early age at onset, and occurrence in multiple generations [66]. Most breast cancer cases are sporadic and not associated with high penetrance gene mutations.

2.4.2 Genetic Polymorphisms

Genetic polymorphisms may account for why some people are more sensitive than others to environmental carcinogens such as exogenous estrogens and alcohol. A large number of genetic variants have been reported to be associated with breast cancer risk but relatively few low-penetrance polymorphisms have been consistently associated with the disease [67]. Most breast cancer susceptibility loci identified in candidate gene studies have not been confirmed [63]. Single
nucleotide polymorphisms (SNPs) of the XRCC2 and XRCC3 genes, which code for proteins that play a role in the homologous recombination of DNA double-strand breaks, have been shown to influence breast cancer risk. These include XRCC2 rs3218536 and rs3218536 [67–69]. A variant of the caspase 8 gene (CASP8) has been convincingly associated with breast cancer risk [63]. Caspase 8 is a protease that is involved in the initiation of programmed cell death (apoptosis) following DNA damage [70].

2.4.3 BRCA Gene Mutations

Mutations in the BRCA1 gene, which is located on chromosome 17q, have been identified as causes of predisposition to breast, ovarian, and other cancers. The BRCA2 gene is located on chromosome 13q. BRCA1 and BRCA2 are expressed in breast, ovarian, and other tissues and play a key role in the repair of double-stranded DNA breaks in the cell nucleus. BRCA1 and BRCA2 mutations account for about 15–20 % of familial breast cancers [71]. Women who carry BRCA1 and BRCA2 mutations have an estimated 40 % to 87 % risk of breast cancer by age 70, although these risks are modified by other factors [72, 73]. There is considerable variability in the age of onset of cancer and the site of cancer across populations [74]. Most of the deleterious mutations in the BRCA1 and BRCA2 genes are small deletions or insertions that result in the translation of a truncated protein [63].

Genetic variants and gene–gene interactions that account for inter-individual variation in DNA repair capacity influence risk of breast cancer [74]. These include variants in the CHEK2, PALB2, and ATM genes, which, like BRCA1 and BRCA2, play a role in DNA repair mechanisms and help to maintain chromosomal stability [63]. Studies have suggested that genomic variation at multiple loci modify breast cancer risk in women who carry BRCA1 mutations [75]. Some of these loci are known to encode proteins that interact biologically with BRCA1 [63]. Candidate gene studies suggest that homozygosity for the RAD51 135G > C allele is associated with breast cancer risk in women who carry BRCA2 gene mutations [76]. Interacting with BRCA1, BRCA2, and ATM at the cellular level, RAD51 is part of a protein complex that plays a role in the repair of double-strand DNA breaks. Genome-wide association studies carried out in general populations have identified additional genetic variants that are associated with breast cancer risk among BRCA1 and BRCA2 mutation carriers.

Other high-penetrance genetic mutations that increase breast cancer risk, and which are rare in the general population, include TP53 germ-line mutations (found in Li-Fraumeni cancer syndrome), PTEN mutations (Cowden syndrome), and STK1 mutations (Peutz-Jegher syndrome) [63].
2.5 Summary and Conclusions

This chapter has summarized the substantial epidemiologic literature on environmental and genetic risk factors for breast cancer in women. Breast cancer risk factors that have been well-established by epidemiologic studies include race, ethnicity, family history of cancer, and genetic variants, as well as modifiable exposures such as increased alcohol consumption, physical inactivity, exogenous hormones, and certain female reproductive factors such as younger age at menarche, nulliparity, and older age at first full-term pregnancy. There is increasing evidence that breast cancer is a heterogeneous disease and that subtypes such as triple negative breast cancers may have a distinct etiology. Epidemiologic studies, family studies, and genome-wide association studies have identified several genetic variants and rare but moderate-to-high penetrance gene mutations that account for some cases of breast cancer. These include genetic variants of genes involved in DNA repair and the homologous recombination of DNA double-stranded breaks. However, the etiology of many breast cancer cases in the population remains unknown.

References


Breast Cancer Metastasis and Drug Resistance
Progress and Prospects
Ahmad, A. (Ed.)
2013, XII, 416 p., Hardcover