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Review article

EPIDEMIOLOGY AND RISK FACTORS OF BREAST CANCER: A GLOBAL PERSPECTIVE ON INCIDENCE, MORTALITY, AND PREVENTION STRATEGIES

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Abstract: *Breast cancer is the most prevalent malignancy among women worldwide, contributing significantly to global cancer mortality. This review provides a detailed examination of the epidemiological trends, molecular subtypes, and risk factors associated with breast cancer, with a focus on disparities in incidence, mortality, and survival across populations. Incidence rates are highest in developed regions, attributed to lifestyle and environmental factors, while mortality rates are disproportionately higher in developing countries due to limited healthcare access and aggressive tumor biology. The analysis highlights the pivotal role of genetic predispositions, such as BRCA mutations, alongside modifiable risk factors, including physical inactivity, obesity, alcohol consumption, and radiation exposure. Hormonal influences, reproductive behaviors, and dietary patterns further modulate individual risk profiles. Emerging evidence underscores the impact of socioeconomic disparities and ethnicity on breast cancer outcomes, particularly among African American and Hispanic women, who often present with more aggressive triple-negative subtypes and worse prognoses. Advancements in early detection, such as widespread mammography, have improved survival rates in developed countries, though challenges persist in low-resource settings. The review emphasizes the significance of understanding molecular subtypes—Luminal A, Luminal B, HER2-enriched, and triple-negative breast cancer—and their implications for targeted therapies. Innovations in genetic screening, personalized medicine, and lifestyle interventions are poised to transform prevention and treatment strategies globally. This review underscores the necessity of addressing healthcare inequities, promoting lifestyle modifications, and advancing molecular research to reduce the global burden of breast cancer. Future efforts should focus on integrating public health initiatives, enhancing access to diagnostic tools, and developing cost-effective therapies tailored to diverse populations. Bridging the gap between resource-rich and resource-limited regions is imperative for achieving equity in breast cancer care and outcomes.*

Keywords: Breast Cancer Epidemiology, Genetic Risk Factors, Molecular Subtypes, Lifestyle Modifications, Healthcare Disparities.

Introduction

The Surveillance, Epidemiology, and End Results (SEER) program has been a great resource for researchers investigating the epidemiology of breast cancer in the United States, and it is the most comprehensive collection of information on incidence, prevalence, and mortality (1). Breast cancer claimed the lives of more than 39,000 men and women in the United States in 2012, with more than 229,000 new diagnoses in the same year. Every year, an estimated 1.4 million women worldwide are diagnosed with breast cancer while the death s reported were 458,000 (2). Breast cancer is currently the most common malignancy in Chinese women, and it is also the sixth largest cause of death. By 2008, China's incidence of breast cancer had reached such astounding proportions that it accounted for 12.2 percent of worldwide cases and 9.6 percent of associated fatalities (3).

In 2010, it was projected that 2.8 million women in the United States had previously been diagnosed with breast cancer, including both active patients and those who had previously been treated. Breast cancer incidence in the United States has historically climbed at a rate of little more than 1% per year until the 1980s, when it spiked due to greater use of screening mammography. In the 1990s, incidence remained relatively consistent, and in the 2000s, incidence fell somewhat; this fall is thought to be due to a decrease in the use of postmenopausal hormone replacement therapy (HRT). Since 2004, the rate of occurrence has been consistent (4). During the 1980s and 1990s, the rate of in situ breast cancer incidence increased dramatically, owing partly to increased mammography screening. Women above the age of 50 had a higher rise in incidence than women under the age of 50. In situ breast

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cancer rates have been stable among women 50 and older since 2000, and among younger women since 2007.

These patterns are most likely mirrored by mammography screening rates, which peaked in 2000 and subsequently stabilized at a somewhat lower rate after 2005 (5). Breast cancer is the most frequent cancer in women worldwide. Breast cancer was detected in 1.7 million new cases in 2012, accounting for 25% of all female cancers (6). Female breast cancer is most commonly diagnosed in women between the ages of 55 and 64, with a median age of 61 at diagnosis. Breast cancer affects less than 5% of women under the age of 40, and the risk grows with age, as it does with most cancers. After menopause, however, the rate of growth slows down (7). Numerous research have looked at contributing factors such as socioeconomic level, health-care access, and genetics. Poor outcomes are partly caused by socioeconomic and health-care access disparities but tumor biology that is more aggressive also plays a role. When socioeconomic considerations are taken into account, African American ethnicity is linked to a 1.19 risk of breast cancer death (8). Black women are more likely to be diagnosed with advanced-stage cancer, and triple-negative tumors harm them disproportionately (9).

Despite having a lower overall incidence of breast cancer, they are more likely to be diagnosed before the age of 45 than white women. These findings show that socioeconomic variables, in combination with differences in tumor biology in black women, play a role in the observed survival differential (10). Breast cancer is the most prevalent cause of cancer mortality among women living in underdeveloped nations, despite the lower reported prevalence. With the "Westernization" of poorer nations, cancer incidence patterns are anticipated to come to resemble those found in more developed countries, resulting in a rise in worldwide breast cancer incidence (11). Regardless of the fact that breast cancer is becoming more common over the world, there are major disparities in incidence rates between affluent and poor nations. More developed regions continue to have the greatest death rates, whereas less developed countries have substantially higher mortality rates. For In Western Europe, for example, the incidence of breast cancer is [90]. Annually, there are 30 new instances per 100,000 women, compared to 30 in the previous year. Despite the fact that the breast cancer rate in eastern Africa is low (per 100,000), These two regions have similar cancer death rates (12).

Mortality

In the United States, breast cancer mortality has reduced by an average of 0.6 percent every year since 1950, for a total reduction of more than 34 percent (1). Since about the age of 57, when white mortality surpasses that of African Americans, Americans had greater age-specific mortality (11). Relative survival has grown considerably during the last five years, from 60% in 1950 to 1954 to over 92 percent in 2003 to 2009. Despite steady to slightly increasing incidence, breast cancer mortality in the United States decreased by 2.3 percent between 2004 and 2008 (1). According to SEER statistics from the 2000s, the incidence (per 100,000) in the white population was 127.4. The overall death rate was 12.3 per 100,000, with a 5-year survival rate of 90.4 percent. The incidence rate in the black population was 121.4 percent. The overall death rate was 18.2%, with a 5-year survival rate of 78.6%. SEER capturing sites have lately increased in number in order to boost statistics on other minority populations, such as Hispanics. In comparison to white and black women, Hispanic women had a lower incidence and fatality rate. The incidence rate was 90.8 per 100,000, with a total fatality rate of 14.8.

Despite these positive statistics, studies show that Hispanic women are diagnosed at a younger age and, like black women, have a higher probability of developing the triple negative phenotype (13). Breast cancer is currently the most common malignancy in Chinese women, and it is also the sixth largest cause of death. By 2008, China's incidence of breast cancer had reached such astounding proportions that it accounted for 12.2 percent of worldwide cases and 9.6 percent of associated fatalities. (3). Although age and tumor size are taken into account, African Americans have a higher chance of recurrence of breast cancer. Unsurprisingly, a multivariate analysis indicated that black women had the greatest 7-year actuarial risk of mortality from stage I cancer 6.2% when compared to white women was 3.0%. The disparity in mortality has been seen to be widening (14).

Table 1: Breast cancer incident and mortality rate among young women in 2018 in countries from world area (Sopik., 2021).

World area Countries	**% of world**	**Breast cancer incident (0-39 age)**			**Breast cancer mortality (0-39 age)**			**M:I Ratio ASR**
		Case %	**ASR**	**Cum.risk %**	**Death %**	**ASR**	**Cum.risk %**	
Asia	59.5	29,141 (52.9)	7.1	0.38	22,230 (46.9)	1.2	0.07	0.17
Americas	13.3	38,849 (15.9)	9.7	0.52	4,853 (10.8)	1.2	0.07	0.12
Africa	16.9	41,493 (17.0)	9.2	0.49	14,632 (32.6)	3.2	0.18	0.35
Europe	9.8	32,453 (13.3)	11.7	0.63	2885 (6.4)	1.0	0.06	0.09
South America Central America	5.6	17,375 (7.1)	9.6	0.52	2539 (5.7)	1.4	0.08	0.15
Northern America	2.3	5304 (2.2)	7.2	0.39	747 (1.7)	1.0	0.06	0.14

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	4.8	14,736 (6.0)	11.3	0.61	1186 (2.6)	0.9	0.05	0.08
Southern Europe Eastern Europe Western Europe Northern Europep	2.0	7384 (3.0)	14.3	0.77	538 (1.2)	0.99	0.06	0.07
	3.8	10,259 (4.2)	8.3	0.45	1293 (2.9)	1.0	0.06	0.12
	2.6	9877 (4.0)	15.3	0.82	685 (1.5)	1.0	0.06	0.07
	1.4	4933 (2.0)	13.2	0.72	369 (0.8)	0.98	0.05	0.07
Southern Africa Eastern Africa Western Africa Northern Africa Middle Africa	0.9	2264 (0.9)	8.1	0.43	504 (1.1)	1.8	0.10	0.22
	5.7	11,231 (4.6)	7.5	0.39%	4528 (10.1)	3.1	0.17	0.41
	5.0	12,272 (5.0)	9.8	0.52	4837 (10.8)	3.9	0.21	0.40
	3.1	11,081 (4.5)	11.5	0.61	2761 (6.2)	2.9	0.15	0.25
	2.2	4645 (1.9)	8.6	0.45	2002 (4.5)	3.8	0.21	0.44
Eastern Asia South Eastern Asia Western Asia South Central Asia	21.7	58,865 (23.3)	9.0	0.48	2967 (6.6)	0.47	0.03	0.05
	8.6	18,769 (7.7)	7.0	0.37	3969 (8.9)	1.5	0.08	0.21
	3.5	10,370 (4.3)	9.8	0.52	1979 (4.4)	1.8	0.10	0.18
	25.7	43,137 (17.7)	5.4	0.29	13,315 (29.7)	1.7	0.09	0.31

Lifestyle and risk factors

A hereditary genetic mutation is responsible for less than 10% of breast cancers. Environmental, reproductive, and lifestyle variables, some of which are theoretically changeable, are more typically linked to breast cancer.

- Physical activities
- Radiation exposure
- Alcohol intake
- Smoking
- Weight
- Dietary factors

Table 2: Epidemiologic Risk Factors for Breast Cancer

Characteristics	Menopausal Status	Estimate of Effect	Reference
Behavioral Factors			Ellison et al., 2001
Body mass index	Postmenopausal	RR 1.27 (1.03–1.55)	
Weight	Postmenopausal	RR 1.25 (1.02–1.52)	
Height	Premenopausal Postmenopausal	RR 1.42 (0.95–2.12) RR 1.28 (0.94–1.76)	
Alcohol use	Both	RR 1.10 (1.06–1.14)	
Smoking	Postmenopausal	RR 1.5 (1.2–1.9)	Cui et al., 2006
Genetic Factors			
BRCA1 mutation	Both	Lifetime risk 50%–73% by age 50 and 65%–87% by age 70	Ban and Godellas, 2014
BRCA2 mutation	Both	Lifetime risk 59% by age 50 and 82% by age 70	
Environmental Factors			
Ionizing radiation	Both	RR varies depending on age at exposure: RR = 9 at age 0–4; RR = 2 at age 35–39	Zhang et al., 2020
Dietary Factors			
Saturated fat intake	Both	RR 1.19 (1.06–1.35)	Boyd et al., 2003
Meat Intake	Both	RR 1.17 (1.06–1.29)	Cui et al., 2006

Physical Activities

Several studies have found that physical exercise, especially in adulthood, lowers the incidence of breast cancer. The stated degree of this impact varied greatly between observational and case-control studies, ranging from 10% to 50% risk decrease with frequent moderate to strenuous exercise (15). A meta-analysis of prospective trials reveals a relatively moderate impact, with a relative risk of roughly 10% to 12% for patients who exercise regularly. There

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appears to be a dose-dependent impact, with the benefit being greater for premenopausal women of normal weight and for cancers that are ER/PR negative (16). Scientific literature research is looking at the impact of physical exercise on breast cancer recurrence studies reveal a reduction in overall mortality (from all causes) and a possible protective effect against ER/PR-negative tumor recurrence (17).

Regular physical exercise lowers the risk of breast cancer. Women who frequently engaged in intense physical activity at the age of 35 had a 14 percent lower risk of breast cancer, according to a secondary analysis of the Women's Health Initiative Cohort Study. Furthermore, the reduction in risk is larger with more hours of exercise (18). The reduction in body fat associated with decreased peripheral conversion of androgens to estrogens via the enzyme aromatase is one of the postulated explanations for the link between physical exercise and lower breast cancer risk. Furthermore, physical exercise may increase the quantity of sex hormone–binding globulin in the blood, lowering the overall amount of free estrogen in circulation. Finally, exercise has been proven to lower insulin levels as well as other growth factors. (11). Physical activity's effects on body composition, insulin resistance, and circulating levels of sex steroid hormones are all conceivable biological causes (19). Particularly in comparison to inactive women, women who engaged in regular strenuous physical activity at age 35 had a 14 percent lower risk of breast cancer (RR = 0.86, 95 percent CI 0.78–0.95) in the Women's Health Initiative Cohort Study, which included 74,171 women aged 50–79 years recruited by 40 United States clinical centers (20). The bulk of epidemiologic research that looked at the link between physical activity and the risk of breast cancer looked at exercise in adults. Physical exercise during childhood and adolescence has also been linked to a lower incidence of breast cancer in recent research (21).

Radiation Exposure

Substantial radiation exposure, even from medical treatments, is an established risk factor for breast cancer. Women who are exposed when they are young (20 or less) are at a greater risk than women who are exposed after the age of 40 (22). There is a dose-response association between the quantity of exposure and the risk of breast cancer in women who were exposed before the age of 40. Breast cancer does not appear in women who have had considerable radiation exposure until their third decade, but the increased risk remains for the rest of their lives (23). This increased risk is well-documented among Hodgkin lymphoma survivors; a 25-year-old woman treated with 40 Gy of radiation has a 29 percent probability of developing breast cancer by the age of 55 (24). Although data supports a relationship with high cumulative exposure owing to recurrent imaging conducted at a younger age, it is still debated whether low-dose ionizing radiation exposure through chest radiography or mammography affects breast cancer risk (25). The higher risk is likely to be connected to the younger breast tissue undergoing fast cell proliferation around the time of puberty. (26).

Alcohol intake

High alcohol consumption has been linked to an increased risk of breast cancer. Women who consume 3 to 4 servings of alcohol per day had a 32 percent higher chance of developing breast cancer than nondrinkers. This is a linear risk association, with each additional serving of alcohol drank per day raising the risk by 7% to 9% (1). Low levels of alcohol use are linked to a minor increase in risk (RR 1.15 for 3–6 servings of alcohol per week), with cumulative alcohol consumption being the most consistent metric. Alcohol use both early and late in life, as well as binge drinking, are all independent risk factors (27). Despite controversy, the bulk of epidemiological research conducted over the last three decades show a persistent link between alcohol use and breast cancer. Women who drank 35 to 44 g of alcohol per day had a relative risk of breast cancer of 1.32, while women who drank at least 45 g per day had a related risk of 1.46, according to a joint reanalysis of 53 global epidemiological studies of breast cancer. This danger was discovered in both smokers and nonsmokers. Race, education, family history, nursing, and hormone usage were also shown to have no effect on the outcomes. According to this pooled research, each additional 10 g of breast tissue raises the risk of breast cancer by 7% (11). Consuming 15 to 30 g of alcohol per day (1 or 2 drinks) was shown to be related with a 33 percent increase in the lifetime risk of breast cancer in a large population-based analysis of 1508 breast cancer cases and 1556 controls, although there was no link between breast cancer and present alcohol use. Lighter alcohol consumption, as well as, counterintuitively, greater alcohol consumption of >30 g, were not linked to an increased risk. This risk was unaffected by the type of alcohol consumed or the frequency with which it was consumed, however it was higher in women with a BMI of 25 (28). A study of women in Southern France found no evidence of a link between drinking and breast cancer. When compared to non-wine drinkers, women who consumed 10 to 12 g of wine per day had a reduced risk (OR= 0.51).

The risk of breast cancer rose when drinking more than 12 g of wine per day, however the link was not statistically significant (Bessaoud and Daures, 2008). The pathways associated to the creation and activation of breast cancer are among the mechanisms for the function of alcohol in carcinogenesis. Several carcinogens are contained in alcoholic drinks or formed by alcohol metabolism, including acetaldehyde, benzene, and N-nitrosodimethylamine (29). Alcohol can indeed affect hormone levels by raising circulating estrogen metabolites and accelerating the conversion of androgens to estrogens by suppressing hepatic estrogen metabolism (30). Alcohol can also depress immunological function, enhance cell invasion and migration, boost cell proliferation, hinder DNA repair, and suppress immune function (31). Observational data from postmenopausal women who took part in the Nurses' Health Study support the notion that drinking alcohol raises the risk of breast cancer through a hormonal mechanism. Breast cancer risk was almost 30% greater in women who had been using postmenopausal hormones for 5 years or more and did not drink alcohol (RR 1.32; 95 percent CI 1.05–1.66).

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Those who never used postmenopausal hormones but drank 1.5 to 2 drinks per day or more had a non-significantly higher risk of 28 percent. Breast cancer risk was approximately double that of nondrinking nonusers of postmenopausal hormones (RR 1.99; 95 percent CI 1.42–2.79) among current users of postmenopausal hormones who consumed 20 or more grams of alcohol daily for about or more than 5 years (5). The effects of alcohol on circulating estrogen levels are one of the proposed biological processes. In the Nurses' Health Study II, Ja Kim et al looked at the link between alcohol intake and breast cancer risk in younger women. Overall, alcohol use was not linked to an increased risk of breast cancer (multivariate hazard ratio = 1.07, 95 percent confidence interval 0.94 1.22 for 10 g/day intake vs. nondrinkers). However, when the association was stratified by family history and folate intake, individuals with a positive family history and a folate intake of 400 g/day had a positive connection with breast cancer with multivariate hazard ratio of 1.82, 95 percent CI 1.06– 3.12, p-trend is 0.08 (32).

Smoking

The link between smoking and breast cancer is still a mystery. According to several research, smoking raises the risk of breast cancer in women, especially when they start smoking early in life and continue to smoke for a long time (33). Indeed, the Surgeon General's study on cigarette smoking in 2004 found no consistent evidence of a link between cigarette smoking and breast cancer (28). The Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk published a thorough study in 2009 that focused on length and timing of exposure, genetic susceptibility, and possible confounders, unlike previous studies. The Surgeon General's 2014 study states that ever-smoking is related with a substantial increase in RR of roughly 10% based on 22 cohort reports published before 2012 and 27 case control reports published between 2000 and 2011. This impact appears to be higher in current smokers than in past smokers, and it appears to be dose-dependent, with an increase in risk with >20 pack-years (34). Patients who smoke have been observed to have fewer mammograms, which might lead to a higher stage of illness upon diagnosis (11). Furthermore, strong evidence suggests that smoking following a diagnosis worsens the prognosis (Passarelli et al., 2016).

In a review of 11 studies, five found significantly increased ORs of at least 1.5 for passive smokers compared to nonsmokers, and six found significantly increased risk of breast cancer for active smokers compared to nonsmokers, implying a similar strength of association between active and passive smoking and breast cancer risk. Some of the variance in the breast cancer-cigarette smoking link may be due to the effect of age at diagnosis and menopausal state on the sensitivity of breast cells to cigarette smoke exposure (5). Parous women who started smoking within 5 years of menarche and nulliparous women who smoked 20 cigarettes per day or more (sevenfold increase in risk) and for 20 cumulative pack-years or more (OR 7.48; 95 percent CI 1.59–35.2) have a considerably greater (70 percent) risk of breast cancer (35). Active smokers are around 25% more likely than never smokers to die of breast cancer a year before their diagnosis.Those who continue to smoke after being diagnosed are more than 70 percent more likely to die of breast cancer than women who never smoked. Women who quit smoking after being diagnosed had a reduced death rate from breast cancer and pulmonary cancer than women who continue to smoke after being diagnosed (5).

Weight/Obesity

Obesity's impact on breast cancer risk has been widely researched and is dependent on menopausal state. Before menopause, having a high BMI offers considerable preventive advantages, but after menopause, it has a positive link with breast cancer risk. Obese premenopausal women are half as likely as women of normal weight to develop breast cancer, while obese postmenopausal women are 25% more likely to develop breast cancer. A meta-analysis of prospective observational studies found that each 5 kg/m2 increase increased the risk of breast cancer by 12% in postmenopausal women (36). The aromatase enzyme in adipose tissue converts androgens to estrogen, which raises circulating estrogen and so increases breast cancer risk in postmenopausal women. Serum estradiol levels in premenopausal obese women are lower, which explains the protective impact of greater adipose tissue. (1).

BMI appears to be negatively associated to survival. Obese women were more likely than normal weight women to be diagnosed with high-grade tumors (57.1 percent vs. 42.3 percent) and lymphovascular invasion in a study of 818 premenopausal women with nonmetastatic breast cancer followed for a median of 29 months is 79.5 percent vs. 63.9 percent (37). BMI>40 was related with an increased risk of death in both Hispanic and nonHispanic white women in a research by Kwan et al in the California Breast Cancer Survivorship Consortium, but not in Asian or African American women. Biglia and colleagues discovered that a BMI of at least 24 was substantially linked with greater tumour size in both premenopausal and postmenopausal breast cancers in a study of 2148 premenopausal and postmenopausal women with breast cancer (38). In comparison to normal or underweight women, obesity is linked to a larger number of metastatic axillary nodes and vascular space invasion (39). When patients with luminal-type (triple-negative) breast cancer were split by breast cancer subtype, OS and DFS were considerably worse in obese patients, and obesity was demonstrated to be an independent predictive factor for luminal-type (ER-positive) breast cancer mortality (37).

Dietary factors

Certain dietary components have been investigated as possible risk factors for breast cancer. Soy has piqued attention since it contains isoflavones (phytestrrogens) with endogenous ER binding activity, and observational studies have shown decreased breast cancer incidence in areas with high soy consumption (40). Surprisingly, increased soy consumption appears to protect Asian people while harming Western populations (41). Several dietary components have been investigated as possible risk factors for breast cancer. Soy has piqued attention since it contains isoflavones (phytestrrogens) with endogenous ER binding activity, and observational studies have shown decreased breast cancer

incidence in areas with high soy consumption. Surprisingly, increased soy consumption appears to protect Asian people while harming Western populations. Future research will focus on the genetic origins of this dichotomous impact (42).

By raising the level of circulating insulin-like growth factor1, a high protein diet may raise the risk of breast cancer (43). A pooled study of eight cohort studies found no link between red meat consumption and the risk of breast cancer (44). Similarly, a more recent prospective research found no evidence of a link between red meat diet and the risk of breast cancer (45). Red meat consumption during early adulthood was linked to an elevated incidence of premenopausal breast cancer in the Nurses' Health Study II (46). A higher intake of carcinogenic byproducts from red meat eating, as well as an increase in hormone intake from exogenous hormones administered to certain cattle, are suggested to explain this probable increase in breast cancer risk (11). Free fatty acids added to plasma may considerably raise levels of estradiol in vitro, and varying amounts of fat ingestion may impact the risk of hormonally dependent breast cancer through modulating levels of circulating estrogens (5).

Hormone Associated Risk Factors

The activating impact of estrogen on hormone receptor–positive cancers, which include luminal A and luminal B subtypes (Table 1), is well documented, and hormone receptor positive breast cancer accounts for almost two-thirds of all occurrences. Two mechanisms have been hypothesized for the carcinogenic effects of estrogen (11). The first includes active estrogen receptor (ER) signaling, which affects gene expression, boosting proliferation and hence the risk of mutations. The oxidative degradation of estrogen into Quinone metabolites is the second route. These Quinone metabolites can then form depurating DNA adducts or be oxidized and reduced into catechol, resulting in reactive oxygen species and DNA damage (47). Human epidermal growth factor 2 (HER2) receptor status for breast cancer patients has been gathered by Surveillance, Epidemiology, and End Results (SEER) registries since 2010. Both hormone receptor (HR) (ER and progesterone receptor [PR]) and HER2 status can be used to classify breast cancer subtypes.

Non-Hispanic (NH) white, NH black, NH Asian Pacific Islander (API), and Hispanic women have different age-specific incidence rates by subtype. (48) Age, race/ethnicity, county-level poverty, registry, stage, Bloom-Richardson grade, tumour size, and nodal status may all be used to characterize hormone receptor and HER2 status distributions. 73 percent of patients with known hormone receptor and HER2 status were HR-positive/HER2-negative, 12 percent were triple-negative (HR-negative/HER2-negative), 10% were HR-positive/HER2-positive, and approximately 5% were HR-negative/HER2-positive; the remaining 12 percent had unknown HR/HER2 status (49). The HR-positive/HER2-negative subtype was most common in NH white women, whereas the triple-negative subtype was more common in NH black women.

Triple-negative patients were more likely to be NH black and Hispanic than HR-positive/HER2-negative patients; HR-positive/HER2-positive patients were more likely to be NH API; and HR-negative/HER2-positive patients were more likely to be NH black, NH API, and Hispanic than HR-positive/HER2-negative patients. Compared to HR-positive/HER2-negative individuals, patients with triple-negative, HR-positive/HER2-positive, and HR-negative/HER2-positive breast cancer were 10% to 30% less likely to be diagnosed at a later age and 6-fold to 20-fold more likely to present with high-grade illness (Anserson et al., 2014). These findings show that various racial/ethnic groups have distinct breast cancer subtypes that appear at diagnosis. The reasons for these disparities have yet to be determined (Volgel, 2018).

Table 3: Molecular Subtypes of Breast Cancer and their clinical characteristics (Rojas and Stuckey, 2016) and (Anderson et al., 2014).

Molecular Subtype	Prevalence (%)	Receptors	Clinical Characteristics
Luminal A	30-70 %	ER and/or PR: positive Her 2: negative Ki-67: low	Slow-growing Less aggressive Low recurrence High survival Best prognosis of all subtypes Respond to endocrine therapy
Luminal B	10-20 %	ER and/or PR: positive Her 2: positive	High proliferation rates Worse prognosis than Luminal A Respond to endocrine therapy
Her 2-type	5-15 %	ER and PR: negative Her 2: positive	Tend to grow and spread more aggressively More likely to be high grade and node positive Poor short-term survival Targeted therapies exist
Triple negative (basal-like)	15-20 %	ER and PR: negative Her 2: negative	High histologic grade Higher rates of distant recurrence after surgery Poor short-term prognosis. Lack targeted therapy

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Reproductive Risk Factors

Early menarche and late menopause have been linked to an increased risk of breast cancer, but premenopausal oophorectomy has been linked to a lower risk. An increased risk has been linked to late age at first and perhaps final full-term pregnancy; the risk diminishes with increasing parity. Breastfeeding is also linked to a lower incidence of breast cancer (50).On every 1-year rise in age at menarche, the risk of premenopausal breast cancer drops by around 9% (95 percent CI 7 percent –11 percent), but the risk of postmenopausal breast cancer decreases by only about 4% (95 percent CI 2 percent –5 percent). Breast cancer risk rises by 5% (95 percent CI 5%–6%) each year for cancers detected before menopause and by 3% (95 percent CI 2 percent–4%) for cancers diagnosed after menopause with increasing age at first full-term pregnancy. Each full-term pregnancy was linked to a 3% (95 percent CI 1%–6%) reduction in the risk of breast cancer diagnosed before menopause, compared to a 12% (95 percent CI 10%–14%) reduction in the risk of breast cancer diagnosed afterwards (51).

Genetic Risk Factors

Breast cancer runs in the family; women who have a mother or sister who has had the disease are twice as likely as the general population. Early start of illness, bilateral disease, or a male cousin with the condition are all additional familial risk factors that point to a genetic susceptibility. This risk is due to the inheritance of high-risk genes.

BRCA Gene Mutation

BRCA1 gene mutations, which are found on chromosome 17q, have been linked to an increased risk of breast, ovarian, and other cancers. On chromosome 13q, the BRCA2 gene is found. Breast, ovarian, and other tissues express BRCA1 and BRCA2, which are involved in the repair of double-stranded DNA breaks in the cell nucleus. The majority of the harmful mutations in the BRCA1 and BRCA2 genes are minor deletions or insertions that cause a truncated protein to be translated (52). About 15–20 percent of family breast cancers are caused by BRCA1 and BRCA2 mutations (53). Women with BRCA1 and BRCA2 mutations have a 40–87 percent chance of developing breast cancer by the age of 70, albeit these chances are influenced by other variables (54).
Across populations, the age of cancer onset and the location of cancer are very variable (55). Kuchenbaecker with his co-workers used data from the International BRCA1/2 Carrier Cohort Study, the Breast Cancer Family Registry, and the Kathleen Cuningham Foundation Consortium for Research into Familial Breast Cancer to look at the risks of breast and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. By the age of 80, BRCA1 carriers had a cumulative breast cancer risk of 72 percent (95 percent CI 65–79 percent) and BRCA2 carriers had a cumulative breast cancer risk of 69 percent (95 percent CI 61–77 percent). For contralateral breast cancer, the cumulative risk was 40% (95 percent CI 35–45 percent) for BRCA1 carriers and 26% (95 percent CI 20–33 percent) for BRCA2 carriers 20 years following breast cancer diagnosis. Breast cancer risk is influenced by genetic variations and gene–gene interactions that account for inter-individual heterogeneity in DNA repair ability (56).
The variants in the APEX1, CHEK2, PALB2, ATM, and XPD genes, which, like BRCA1 and BRCA2, play a role in DNA repair pathways and contribute to chromosomal stability, are among them (57). Breast cancer risk in women with BRCA1 mutations appears to be modified by genetic variation at many loci, according to studies (58). Some of these genes are known to code for proteins that interact with BRCA1 physiologically (57). According to candidate gene research, homozygosity for the RAD51 135G [C allele is linked to a higher risk of breast cancer in women with BRCA2 gene mutations (57). At the cellular level, RAD51 interacts with BRCA1, BRCA2, and ATM to form a protein complex that aids in the repair of double-strand DNA breaks. Additional genetic variants linked to breast cancer risk among BRCA1 and BRCA2 mutation carriers have been discovered through genome-wide association studies in general populations (20) TP53 germ-line mutations (found in Li-Fraumeni cancer syndrome), PTEN mutations (Cowden syndrome), and STK1 mutations are further high-penetrance genetic variants that enhance breast cancer risk and are uncommon in the general population as Peutz-Jegher syndrome (57).

Survival of BRCA Patients

A 20-year analysis of research addressing breast cancer prognosis in BRCA mutation carriers found no indication of a substantial difference in OS between individuals with spontaneous and BRCA-associated breast cancer (11). However, the majority of studies found an increased risk of contralateral second primary breast cancer, with 10-year risks ranging from 20% to 40%. Within the first five years after diagnosis, however, the probability of recurrence was shown to be identical in both carriers and noncarriers (59).

P53/Li-Fraumeni syndrome

P53 is another high-penetrance gene that has been linked to the development of breast cancer. P53 mutations are linked to Li-Fraumeni syndrome (LFS), which is linked to an increased risk of breast cancer, leukaemia, and lung and brain cancers (60). By the age of 60, women with LFS had a 50% chance of developing breast cancer. (61). Up to 7% of all breast cancers detected in women under the age of 40 are thought to be caused by LFS or P53 mutations. Breast tumours in LFS patients are mainly ER/PR/HER2-positive (Mehlem et al., 2012).

Low-penetrance genes

There have been other additional genes linked to an increased risk of breast cancer. (1). These genes have a lower penetrance and contribute less to the disease burden of breast cancer than the ones listed above (62). Many are involved in DNA repair and genomic integrity maintenance processes, as well as cell-cycle checkpoints. ATM, BRIP1, CHEK2, NBS1, PALB2, and RAD50 mutations have been linked to a 2- to 4-fold higher risk of breast cancer (63).

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PTEN/Cowden syndrome

PTEN hamartoma tumor syndrome/Cowden syndrome is caused by mutations in the PTEN gene and is characterized by the formation of many hamartomas as well as an increased risk of thyroid, endometrial, and breast cancer (61). PTEN is an autosomal-dominant tumour suppressor gene that is involved in the MAPK/mTOR pathways. Individuals with germline PTEN mutations have an estimated lifetime risk of breast cancer of 85 percent, despite the low incidence of the mutation (64).

Conclusion:

Breast cancer remains the most prevalent cancer among women worldwide, presenting significant challenges due to its complex etiology and diverse risk factors. This review highlights disparities in breast cancer incidence, mortality, and survival rates between developed and developing regions. While developed nations report higher incidence rates due to lifestyle changes and better screening programs, developing countries face disproportionately higher mortality rates driven by late diagnoses, limited healthcare access, and aggressive tumor subtypes. Genetic factors, particularly BRCA mutations, play a pivotal role in increasing susceptibility, alongside modifiable lifestyle factors such as physical inactivity, obesity, alcohol consumption, and radiation exposure. Socioeconomic and healthcare disparities further exacerbate these outcomes, with African American and Hispanic women more likely to present with aggressive subtypes like triple-negative breast cancer, leading to poorer prognoses. Moreover, molecular subtypes, including Luminal A, Luminal B, HER2-positive, and triple-negative breast cancers, underline the necessity for personalized treatment approaches. Advancements in early detection and treatment have contributed to declining mortality rates in high-resource settings, yet low-resource regions continue to lag. This underscores the urgent need for global initiatives to improve access to preventive care, screening, and innovative therapies. Promoting public health awareness, addressing socioeconomic inequities, and investing in molecular research are critical to reducing the global burden of breast cancer. In conclusion, an integrative approach encompassing prevention, equitable healthcare delivery, and advancements in precision medicine is essential for improving outcomes and achieving global equity in breast cancer care.

Declarations

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All data generated or analyzed during the study are included in the manuscript.
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Conflict of interest

The authors declared an absence of conflict of interest.

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