Review Article

Breast cancer: Epidemiology, risk factors and screening

Hangcheng Xu, Binghe Xu

Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China

Correspondence to: Binghe Xu, MD. Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 17 Panjiayuan Nanli, Beijing 100021, China. Email: xubh@cicams.ac.cn.

Abstract

Breast cancer is a global health concern with a significant impact on the well-being of women. Worldwide, the past several decades have witnessed changes in the incidence and mortality of breast cancer. Additionally, epidemiological data reveal distinct geographic and demographic disparities globally. A range of modifiable and non-modifiable risk factors are established as being associated with an increased risk of developing breast cancer. This review discusses genetic, hormonal, behavioral, environmental, and breast-related risk factors. Screening plays a critical role in the effective management of breast cancer. Various screening modalities, including mammography, ultrasound, magnetic resonance imaging (MRI), and physical examination, have different applications, and a combination of these modalities is applied in practice. Current screening recommendations are based on factors including age and risk, with a significant emphasis on minimizing potential harms to achieve an optimal benefits-to-harms ratio. This review provides a comprehensive insight into the epidemiology, risk factors, and screening of breast cancer. Understanding these elements is crucial for improving breast cancer management and reducing its burden on affected individuals and healthcare systems.

Keywords: Breast neoplasms; epidemiology; mass screening; risk factors

Submitted Nov 29, 2023. Accepted for publication Dec 14, 2023.
doi: 10.21147/j.issn.1000-9604.2023.06.02
View this article at: https://doi.org/10.21147/j.issn.1000-9604.2023.06.02

Introduction

Breast cancer is a disease of great heterogeneity, with a multifaceted etiology encompassing genetic and nongenetic factors (1). As recent global cancer statistics indicate, breast cancer has surpassed lung cancer and become the most frequently diagnosed cancer worldwide, accounting for 11.7% of new cancer cases in 2020 (2). Thus, breast cancer remains a significant global health concern despite the rapid advances in this field.

The epidemiology of breast cancer has been deeply and constantly investigated over the decades (3,4). Understanding the epidemiological characteristics of breast cancer including its incidence, prevalence, and mortality across different demographic and geographic aspects, as well as identifying the risk factors, could facilitate the development of proper public health policies. Screening is a key part of the overall management of breast cancer, which can detect breast cancer at an early stage, thereby reducing the associated mortality dramatically (5). And the emerging novel approaches for detection necessitate more personalized options to weigh pros and cons of screening (6). In this review, we summarize the current state of knowledge on the epidemiology and screening of breast cancer by synthesizing recent findings, and discuss the challenges and future directions in this field.

Epidemiology

Global incidence and mortality

Over the course of time, the global incidence of breast

cancer increased rapidly during the 1980s and 1990s (7), which was largely due to enhanced detection (8). Then, a sharp drop occurred in the US population as the use of hormone replacement therapy (HRT) decreased (9). Since 2007, the burden of breast cancer rose again (10,11) and this trend continues today. The explanations might encompass increased body mass index (BMI) and decreased birth rate (12). During the recent decade (2010–2019), the incidence of breast cancer increased at a rate of 0.5% annually (13). The local-stage disease contributed largely to the increase. Population growth and aging were also believed to be key factors (14) since the change in age-standardized rate (ASR) was not obvious. To sum up, the past three decades witnessed a 128% increase in the total number of incident cases worldwide (15). In 2020, female breast cancer became the most commonly diagnosed cancer globally for the first time, with an estimated 2.26 million new cases reported (2). The most recent prediction suggests that by 2040, the global burden of breast cancer is expected to increase to over 3 million new cases annually (16).

The mortality rate of breast cancer also fluctuated over the past few decades. From 1970s to 1980s, the mortality rose steadily in most countries (17). After the death rate peaked in the late 1980s, it sharply decreased as the way in which breast cancer was managed changed (18). At this time period, both mass mammography screening and better treatment contributed to the mortality reduction (19). However, in recent years, the decline in mortality has slowed to 1.3%, which could result from the gradual increase in the incidence of breast cancer and the stable prevalence of screening (13). The latest global statistics showed that breast cancer was the leading cause of cancer-related mortality among women, ranking fifth in overall cancer deaths (2). By 2030, the mortality rate from lung cancer in women is expected to surpass that of breast cancer in some developed countries (20).

Geographic and demographic disparities

Globally, there exist notable variations across different regions and among various ethnicity, often reflecting a complex interplay of genetic, environmental, socio-economic, and healthcare access factors (21). It has been observed that countries with a high human development index (HDI) like Northern America, Australia, and Northern and Western Europe, tend to have a higher incidence of breast cancer compared to those with a lower HDI (22,23). The reasons include a high prevalence of hormonal and lifestyle risk factors on one hand, and increased detection of early disease on the other (2). Even within a single country, the impact of different risk factors on the overall incidence of breast cancer varies geographically (24). Conversely, countries with a lower HDI tend to exhibit higher mortality rates due to limited access to healthcare for their populations (2). For example, the stage at diagnosis of breast cancer tends to be later in countries like those in sub-Saharan Africa, as indicated by a meta-analysis (25).

Race and ethnicity should also be taken into account when interpreting the epidemiology of breast cancer. Various studies have demonstrated significant disparities in breast cancer incidence and mortality across different racial and ethnic groups (26). In the US, compared to White women, the Black women generally have a lower incidence and higher mortality (27), and this disparity has remained stable till now. A mix of factors contribute to this phenomenon, including socioeconomic status and biological heterogeneity (28). During the ongoing pandemic, the impact of COVID-19 has also exhibited racial disparities, with Black women experiencing worse outcomes compared to Non-Hispanic White patients (29).

In China, breast cancer poses as a significant public health issue. As of 2015, it was identified as the most common cancer and one of the leading cause of cancer-related deaths among women in the country (30). Worldwide, the newly diagnosed cases and deaths from breast cancer in China constituted 18.4% and 17.1% of the global totals in 2020, respectively (31). A Bayesian-based predictive model forecasts that this upward trend will persist into the next decade (32). Among the evolving risk factors, high BMI is regarded as the most significant one among Chinese women (33). In brief, the overall landscape of breast cancer in China and Western countries is converging (34).

Clinicopathological variations

The diversity in clinicopathological features of tumors across different regions and ethnicities partly explains the worldwide epidemiological pattern of breast cancer. According to the 2022 breast cancer statistics (13), the overall median age at diagnosis is 62 years. For White women, the median age is 64 years, while it is younger for women of other ethnicities, such as Black women (60 years). In Central China, the age distribution peaks at

45–49 years, while in the US, patients display two age peaks at 60–64 and 80 years (35). The prevalence of breast cancer in younger individuals varies across different regions. In the West, the incidence rate in patients below 40 years old is 4%–5%, compared to a 13% incidence rate in the East (36). An increase in young breast cancer cases has been reported (37).

Regarding molecular subtype, in the US, hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative breast tumors are the most common subtype, comprising 68% of cases, while HR+/HER2+ tumors are the least common, accounting for only 4%. Among different ethnicities in the US, Black women are more likely to be diagnosed with triple-negative breast cancer (TNBC) compared to White women (13), which is associated with aggressive biological behavior. The positive rate of estrogen receptor (ER) is reported to be 59% in Africa (38) and 56.7% in Central China (35), according to different studies. Both African and Asian patients showed an increased prevalence in the HER2-enriched molecular subtypes compared with White patients (39,40). Furthermore, Black women are more likely to be diagnosed at a later stage compared to White and Chinese women, and this trend may be partly due to intrinsic biological factors (41). At the molecular level, significant differences could be detected between different populations. Compared with White women, Asian women exhibited a higher prevalence of *TP53* mutations and elevated immune scores (40). More *TP53* mutations and fewer *PIK3CA* mutations were observed in Black women (39,42). The variation in molecular characteristics partly explains the difference in prognosis across different regions.

Male breast cancer (MBC)

MBC is a rare disease, accounting for less than 1% of all breast cancers (43). The median age at diagnosis of MBC is 63.4 years, which is older than that of female breast cancer (44). The peak incidence of MBC occurs at 71 years old (45). Worldwide, a total of 25,143 men were diagnosed with MBC, and 12,099 men died of MBC in 2019 (46). Like female breast cancer, the incidence of MBC has been on the rise over the last few decades (47), a trend anticipated to continue (33). MBC also exhibited similar distribution pattern across different regions and ethnicities. Previous data suggested that African males had a higher incidence of MBC due to the higher prevalence of endemic infectious diseases that could result in liver damage, which in turn could further elevate the conversion of androgen to estrogen (48).

With regard to its rarity, the study of MBC has largely been informed by data from the Surveillance, Epidemiology, and End Results (SEER) database. MBC usually presents at an advanced stage with a higher tumor grade due to the delays in the diagnosis. Compared to its female breast cancer counterparts, MBC exhibits a higher proportion of ER-positive disease (49) and has worse overall survival (OS) (50). Additionally, MBC displays distinct molecular landscapes. A recent systematic review identified a series of male-specific biomarkers such as STC2, DDX3, and DACH1, beyond the well-established markers (51).

Risk factors

Risk factors play important role in the onset and progression of tumors, and can be categorized into modifiable and non-modifiable factors. Addressing modifiable risk factors can significantly reduce the global cancer burden (52). For breast cancer, there are risk factors common to other cancer types as well as those unique to it (53).

Genetic risk factors

Hereditary breast cancer accounts for approximately 5% to 10% of all breast cancer cases. Individuals with a positive family history, especially those with a first-degree relative affected, are at a significantly increased risk for breast cancer (54). *BRCA1* (17q21) and *BRCA2* (13q13) are two common genetic mutations that are involved in DNA repair by homologous recombination (55). *BRCA1* and *BRCA2* mutations are responsible for 35% and 25% of hereditary breast cancer, respectively (56,57). The prevalence of *BRCA1* and *BRCA2* mutations is relatively high in certain populations like Ashkenazi Jewish (58). Apart from *BRCA1* and *BRCA2*, other high-penetrance genes associated with breast cancer include *PTEN*, *TP53*, *CDH1*, and *STK11*, while moderate-penetrance genes include *CHEK2*, *BRIP1*, *ATM*, and *PALB2* that are involved in the DNA repair and cell cycle control (55). Different genetic mutations observed in patients are associated with certain molecular subtypes of breast cancer (59).

Hormonal risk factors

Estrogen, a steroid hormone, is responsible for developing

women sexual characteristics and plays an important role in the metabolism. However, estrogen and estrogen metabolites also have potential carcinogenic effects, either by acting on ER, affecting cell proliferation and cell cycle progression, or by causing oxidative damage to DNA (60). Thus, abnormally high estrogen levels caused by both endogenous and exogenous sources of estrogen may increase the risk of developing breast cancer (61).

Reproductive patterns

The ages at menarche and menopause are both significant risk factors, as they are associated with the duration of estrogen exposure. Several previous case-control studies and pooled analyses have shown that an age at menarche older than 15 years significantly increases the risk compared to an age at menarche of 12–13 years or younger (62-64). Inversely, early menopause lowers the risk of breast cancer, especially when comparing women who experience menopause at age 55 years or older with those at an age younger than 45 years (53). In addition, menstrual cycle features also affect the breast cancer risk. Short and regular menstrual cycles, which lead to increased lifetime exposure to estrogen and progesterone, are observed more frequently in women with breast cancer than in healthy women (65). Other characteristics, such as the number of menstrual cycles before the first full-term pregnancy and early menstrual regularity, are also associated with breast cancer risk (65,66).

Several factors related to pregnancy play a significant role in modulating the risk of breast cancer. Regarding the age at first childbirth, increasing age seems to elevate the risk of HR-positive breast cancer. Women having their first child at age 30 years or older have a higher risk for breast cancer compared to those aged 25–29 years, but a lower risk compared to nulliparous women (63). A recent study found that this association displays an ethnicity-specific profile (67). The relationship between the age at first birth and the prognosis of breast cancer patients has shown conflicting results (67). The number of pregnancies, including parity and abortions, were also studied. Some findings indicate that parity is associated with a lower risk of HR-positive disease, but not HR-negative disease (64,68). Though pregnancy may increase the risk in the short-term due to transient exposure to high levels of sexual hormones, it exerts protective effects in the long-term (69,70). Early studies reported an association between abortion and subsequent breast cancer risk (71). However, the causal relationship between either induced or spontaneous abortion and breast cancer risk was not confirmed in later, more rigorous studies (72).

Breastfeeding is another well-established factor in reducing breast cancer risk. A large-scale study reported that every 12 months of breastfeeding decreased the breast cancer risk by 4.3% (73). A meta-analysis concluded that breastfeeding could exert protective effects against HR-negative disease. It also observed a reduction of risk in *BRCA1* carriers, but not in *BRCA2* carriers (74). The association between breastfeeding and the risk of HR-positive breast cancer is still unclear (75). The protective effects may be attributed to the biological mechanisms involving the immunological components in breast milk (76), and the regeneration and differentiation of breast cells (77).

Hormone-containing medications

Besides the carcinogenic effects of endogenous hormones, medications containing synthetic versions of estrogen and/or progesterone like oral contraceptives (OC) and HRT that introduce exogenous hormones into the body are also associated with breast cancer.

The use of OC is prevalent among women of reproductive age, especially in western countries. The common dosage form is the combined OC (COC), known for its satisfactory efficacy and safety, which contains synthetic estrogen and progestins (78). Previous evidence concerning the relationship between COC use and breast cancer risk has been inconsistent. A meta-analysis involving more than 150,000 women from 54 studies showed that women who are currently using COC or have used it in the past 10 years had a slightly increased risk of breast cancer compared to never-users (79). Similarly, a more recent large-scale study conducted among Danish women yielded similar findings, although the absolute increase in risk is small (80). However, a case-control study based on US women aged 35–64 years did not support the association (81).

HRT is prescribed to patients experiencing climacteric symptoms during menopause by mimicking the effects of natural hormones. Additionally, long-term HRT has shown several benefits including reducing the risks of coronary heart disease (CHD) and mortality (82). Based on formulation and administration routes, HRT can be categorized into different types (83). It can be composed of estrogen only or combined with progestins, and can be administered orally, transdermally, or topically to alleviate systemic or genitourinary symptoms (84).

The relationship between HRT and breast cancer has been a topic of discussion for many years. The risk assessment regarding breast cancer varies across different studies, types of HRT, and other contributing factors. Previous data from the Women's Health Initiative (WHI) (85) and the Million Women Study (86) established that the risk of breast cancer escalates with the use of HRT. A more recent nested case-control study further substantiated this association, revealing that combined HRT and longer duration present a higher risk (87). A meta-analysis suggested that an elevated risk was displayed across all kinds of molecular subtypes, with the strongest association observed in luminal A breast cancer (75) .

Behavioral and environmental risk factors

Physical activity

Several observational studies have found that greater physical activity were related to lower breast cancer risks (88,89). Dose-response analyses indicated that the higher the level of activity, the lower the risk (90,91). To decipher the causality, Mendelian randomization studies were conducted. The potentially inverse causal relationship between physical activity and risks of breast cancer was supported by the work of Papadimitriou *et al*. (92). Another study by Dixon-Suen *et al*., employing a similar methodology further confirmed the conclusions, with consistent results generated across different molecular subtypes (93). In addition, sedentary behavior is also an independent risk factor for breast cancer, with a linear relationship existing between them (94).

Besides analyzing the overall population of breast cancer patients, researches have also been stratified based on different subgroups. Some studies have discovered menopause-dependent subgroup effects regarding the protective impact of physical activity, with stronger evidence of risk reduction in postmenopausal women compared to premenopausal women (95). In addition to menopausal status, other factors such as BMI, race, HR status, family history, and parity also warrant consideration when discussing the effects of physical activity (96). The potential biologic rationale underlying the beneficial effects of physical activity encompasses the reduction of body fat, leading to decreased exposure to endogenous sex hormones. Other possible mechanisms might include the reduction of insulin and other growth factors, as well as alterations in immune system responses (97).

Body weight

BMI is widely used to quantify body weight and classify somatotype. Overweight is defined as a BMI of 25.0–29.9 kg/m², and obesity as a BMI of 30.0 kg/m² or higher (98). Accumulating data suggest that obesity is related to an increased risk breast cancer in postmenopausal women, especially for ER-positive subtypes. A previous meta-analysis of 10 studies showed that each 5-unit increase in BMI was associated with a 33% greater risk of developing ER-positive and progesterone receptor (PR)-positive tumors (99). Results from WHI clinical trials, which enrolled 67,142 postmenopausal women, revealed that a BMI of 35.0 kg/m² or higher was strongly associated with ER+/PR+ tumors and advanced disease, characterized by tumor size, lymph node involvement, stage, and prognosis (100). Contrarily, weight loss has been shown to exert protective effects in postmenopausal women, suggesting that weight management could be included as a strategy for preventing breast cancer (101). The relationship between BMI and breast cancer risk in premenopausal women is less clear. Several meta-analyses have shown a significant decrease in the risk of developing HR-positive breast cancer (99,102,103). However, an increased risk of developing TNBC has been observed (103). The timing and pattern of weight gain or loss also play important roles in determining their impact on breast cancer risk (104).

Differences in display among women with varying menopausal statuses suggest underlying estrogen-driven mechanisms. In postmenopausal women, excess adiposity elevates estrogen levels, which are primarily derived from the conversion of androgens to estrogen via aromatase (105). Chronic hyperinsulinemia, low-grade inflammation, and oxidative stress associated with obesity are estrogen-independent mechanisms that increase the risk of breast cancer (106).

Diet

Dietary patterns have been identified as important risk factors. The exists complex interplay between diet, metabolism and cancer development. The Western and Mediterranean diets, as two representative dietary patterns, have distinct characteristics and associations with breast cancer risk (107). The Western diet is typically high in calories and low in nutrients. While there is a longstanding debate over the association between saturated fat intake and breast cancer, some studies have found a positive association (108,109), particularly with HR-positive tumors (108), whereas others have not found a significant link

(110,111). Similarly, the role of dietary sugar as a risk factor for breast cancer has yielded inconsistent results (112,113). However, regardless of these mixed findings, high consumption of fats and sugars may contribute to weight gain, leading to overweight or obesity, which is directly related to an increased risk of breast cancer through the pathway mentioned above. The Mediterranean diet, characterized by a high intake of fruits, vegetables, legumes, unrefined cereals, and olive oil, is renowned for its numerous potential health benefits (107). Studies have indicated that adherence to the Mediterranean diet reduces the risk of developing breast cancer in both pre- and postmenopausal women (114), which is consistent across all molecular subtypes (115). The antioxidants in the diet's principal components may be responsible for reduction of oxidative stress and inflammation, thus potentially leading to a lower cancer incidence (116).

Alcohol consumption has been identified as a risk enhancer in breast cancer, with studies demonstrating a dose-response relationship (117). A meta-analysis of 53 studies found that for each daily increase of 10 grams in alcohol consumption, the risk elevated by 7% (118). Even slight drinkers, consuming 12.5 g/d or less, face a 5% increased risk compared to non-drinkers (119). Regarding the molecular subtype, an increased risk of luminal A and HER2-type breast cancer was observed in a large-scale study (120). The mechanisms behind this include hormonal imbalances, particularly in estrogen levels, and the generation of carcinogens during ethanol metabolism (121). A recent study by Zhou *et al*. revealed that epigenetic modifications at several CpG sites also play a role in the pathogenic effect of alcohol on breast cancer (122).

Smoking

Accumulating data indicates a modest but real association between both smoking and second-hand smoke with breast cancer (123). A notable pooled analysis of 14 cohort studies, involving 934,681 participants, found that the risk of breast cancer, particularly ER-positive breast cancer, increases with the duration of smoking before the first birth. This association was observed to be independent of adult alcohol intake (124). Supporting this, another study and meta-analysis drew similar conclusions (125). A linear dose-response relationship between the risk of breast cancer and both the intensity and duration of smoking has been observed (126). The carcinogenic compounds in tobacco smoke, such as polycyclic aromatic hydrocarbons (PAH) and aromatic amines, are absorbed and metabolized by mammary tissues, contributing to the development of breast cancer (127).

Environmental exposures

The environmental risk factors underlying the etiology of breast cancer involves exposure to radiation, chemicals, artificial light, and contamination in air, water, and soil during different windows of susceptibility like prenatal, pubertal, pregnancy, and menopausal periods (128,129).

Radiation exposure is a well-established risk factor for breast cancer. In the Life Span Study of Japanese atomic bomb survivors, both the incidence of female breast cancer (130) and MBC (131) significantly increased. The risk for female breast cancer increases linearly with the dose of ionizing radiation, and this risk is modified by the age at exposure and attained age (130). Numerous studies also suggest a link between radiation used for medical purposes, including diagnostic radiation and radiotherapy, and an increased risk of breast cancer (132). Women survivors of Hodgkin lymphoma (HL) treated with chest radiotherapy at a young age face a breast cancer incidence of 16.6% up to 30 years later (133). In male survivors, the incidence increases dramatically, up to 23-fold compared with the general population over a 40-year period (134).

Chronic exposures to numerous chemicals at younger ages may elevate the risk of developing breast cancer, as indicated by both laboratory and human evidence. Known chemicals of concern include dichlorodiphenyltrichloroethane (DDT), dioxins, perfluorooctane-sulfonamide (PFOSA), and certain air pollutants. These substances are thought to contribute to cancer development either through genotoxic or hormone-altering pathways (135). Additionally, exposure to outdoor light at night (LAN) is being studied as another risk factor for breast cancer. High levels of LAN disrupt nocturnal melatonin secretion and circadian rhythms, potentially promoting mammary carcinogenesis (136). However, the association between LAN and breast cancer risk remains unclear. Some suggest a positive correlation (137), while others do not (138). A recent study by Sweeney *et al*. highlights the need to consider additional environmental factors like NO_2 and noise pollution when discuss the effects of outdoor LAN on breast cancer risk (139).

Breast-related risk factors

Breast density

Breasts are composed of fibrous tissue, glandular tissue, and

fat. Breast density is quantified using mammogram and is characterized by the proportion of fibrous and glandular tissue relative to fatty tissue in the breasts. Nearly half of women aged 40 years and older have dense breasts, which is associated with hereditary factors, productive factors and BMI (140). Women with dense breasts are at a greater risk of breast cancer compared to those with fatty breasts (141,142). This trend remains consistent across different age groups and menopausal statuses (142,143). Dense breast means it hard to detect early breast cancer from mammograms, leading to the delay in the diagnosis and treatment. Furthermore, breast cancer typically originates from epithelial cells, and the dense breast, with its higher amount of epithelial components, evidently increases the likelihood of developing breast cancer (144). However, despite the aggressive biological characteristics of breast cancer associated with dense breasts, no significant difference was detected in mortality between patients with dense breasts and fatty breasts (145).

History of breast lesions

Individuals with a history of breast cancer are at a higher risk of developing a second primary breast cancer. According to a SEER-based analysis of 812,851 women with unilateral breast cancer, there is an annual risk of 0.37% for contralateral invasive breast cancer, which accumulates to 9.9% over 25 years. The risk is higher in Black women and those with ER-negative disease compared to their counterparts (146). Breast cancer patients carrying *BRCA1/2* mutations experience a cumulative risk of 18.4% of a second primary contralateral breast cancer compared to 4.9% for non-carriers (147). Furthermore, pre-invasive breast lesions, including both lobular carcinoma *in situ* (LCIS) and ductal carcinoma *in situ* (DCIS), are associated with increased risks of developing invasive breast cancer even after surgical excision (148,149).

Beyond malignant breast lesions, there are several benign breast diseases (BBD) with high prevalence (150), which could be divided into various categories. Overall, as proliferative activity and atypia increase, so does the risk of developing breast cancer. A study involving 9,087 women over a 15-year follow-up period estimated the relative risks (RR) associated with different types of BBD (151). The RRs for non-proliferative (NP) changes, proliferative disease without atypia (PDWA), and atypical hyperplasia (AH) are 1.27, 1.88, and 4.24, respectively. Additionally, clinical factors such as the time since biopsy, menopausal status, and family history of breast cancer may influence the relationship between these lesions and the risk of breast cancer (152).

Screening

Breast cancer screening, which involves various methods, is part of a secondary prevention strategy for breast cancer, facilitating early detection and treatment. Though the screening is recommended by different guidelines of breast cancer, it is important to balance the benefits and harms of screening and to select suitable screening modality for each patient.

Screening modalities

Mammography

Mammography, first widely adopted in the 1960s (153), continues to be the primary screening tool, as recommended by various global guidelines (154). In this process, the patient's breast tissue is compressed using a plate. Low-energy X-rays, typically ranging from 20 to 30 kVp, penetrate the breast tissues to generate mammograms, which are two-dimensional images. Standard digital mammography (DM) involves acquiring images in both the mediolateral oblique (MLO) and craniocaudal (CC) views. Additional views, such as the mediolateral (ML) view, are also utilized in cases where diagnostic uncertainty exists. Mammograms are effective in identifying various breast abnormalities, including masses, calcifications, and architectural distortions (155). The breast lesions identified in mammograms were categorized using the Breast Imaging Reporting and Data System (BI-RADS), which divides findings into seven categories, ranging from 0 to 6 (156).

The Health Insurance Plan (HIP) study was the first to investigate the efficacy of mass screening in reducing breast cancer mortality. Involving over 60,000 women aged 40–64 years, this study demonstrated a one-third reduction in mortality (157). Subsequently, numerous clinical trials conducted before the 21st century in various countries, including the Swedish Two-County Trial, further confirmed the benefits of mammography in a similar age group (158). A meta-analysis, drawing conclusions from pooled clinical trials and observational studies for women aged 50–69 years, indicated a varied level of mortality risk reduction across different age groups (159). While the Gothenburg breast screening trial (160) and the UK Age trial (161) suggested benefits, the Canadian National Breast

Screening Study-1 (CNBSS-1) (162) and another meta-analysis did not support screening in this age group (159).

Given the challenge of overlapping breast tissues in conventional mammography, digital breast tomosynthesis (DBT) has been developed to address this shortcoming (163). Also known as three-dimensional mammography, DBT creates multiple thin-section images of the breast, providing a clearer view of the breast tissues. This technique has been shown to potentially improve cancer detection and reduce recall rates compared to traditional mammography, as evidenced by several studies (164) and pooled analyses (165). Consequently, the use of DBT is increasing. However, it remains uncertain whether this advanced technique translates into a mortality benefit. The ongoing Tomosynthesis Mammographic Imaging Screening Trial (TMIST) is the first large-scale randomized clinical trial comparing mammography with DBT in reducing the incidence of advanced cancer (166). Additionally, given the increased radiation dose of DBT, synthetic mammography (SM) combined with DBT may be an alternative to DM combined with DBT (167).

Contrast-enhanced mammography (CEM) is another subset of the mammography basing on dual-energy breast exposure. CEM uses contrast agents to depict tumor neovascularity, potentially improving the detection of breast cancers, especially in patients with dense breasts or when evaluating suspicious findings detected by mammography. Studies have indicated that CEM substantially improves sensitivity (ranging from 94% to 100%) and specificity (ranging from 74% to 96%), especially in these scenarios (168). Currently, CEM is recommended as a screening tool for individuals at high risk. Operating in a manner similar to magnetic resonance imaging (MRI), CEM can significantly reduce time and cost, making it viable for widespread use (169). Despite the comparable diagnostic performance between CEM and MRI, a recent meta-analysis indicated that MRI has superior sensitivity and a lower negative likelihood ratio (170). Beyond mass screening, CEM is also employed in preoperative assessments of local disease extent and in monitoring responses to neoadjuvant chemotherapy (169).

Ultrasonography

With the advancement in ultrasound equipment and techniques, breast ultrasound has become increasingly important in breast cancer screening. Recognized for being a non-invasive and radiation-free diagnostic method, it effectively distinguishes cystic from solid lesions and is particularly effective in detecting smaller lesions in women with dense breasts (171). Studies show that, compared to mammography alone, ultrasound enhances both sensitivity and specificity in younger women and those with dense breasts (172).

Breast ultrasound typically serves as a supplementary tool to mammography and physical examination, especially in high-risk groups. A large-scale randomized study demonstrated that adding breast ultrasound to mammography substantially improved diagnostic accuracy (0.91 *vs.* 0.78, P=0.003) in high-risk women (173). According to a meta-analysis, when combined with mammography, pooled sensitivity of breast ultrasound in detecting lesions in women with dense breasts rose from 74% to 96%. However, this combination also saw a decrease in specificity from 93% to 87%, leading to increased recall and biopsy rates (174). Given the operator-dependent nature of hand-held ultrasound and its lack of standardization, the emerging technique of automated whole-breast ultrasound (ABUS) is showing promising prospects. The SomoInsight study, which involved 15,318 women with dense breasts, indicated that adding ABUS to mammography increases the cancer detection rate (175).

MRI

Breast MRI utilizes magnetic fields to produce detailed images of breast tissue, highlighting the morphological and kinetic characteristics of breast lesions. Contrast-enhanced MRI is extensively used in breast cancer management, measuring the extent of disease and assessing the response to neoadjuvant therapy, outperforming other modalities in sensitivity (176).

Compared to mammography, breast MRI excels in detecting small, node-negative invasive cancers (177), potentially improving breast cancer survival rates. Currently, breast MRI is recommended as an adjunct to mammography or ultrasound in high-risk women (178). However, for women at average risk, routine MRI screening is not advised due to a higher incidence of false positives leading to unnecessary biopsies (179). Additionally, challenges such as limited availability, cost-effectiveness, and low adherence limit breast MRI utilization (177). Despite these challenges, emerging evidence supports the use of MRI in the average risk group. A recent meta-analysis of 22 studies showed that MRI is the most effective supplemental modality for detecting cancer in average or intermediate-risk women with dense breasts and negative mammography results (180).

Physical examination

It is estimated that about 5%–10% of breast cancers could be detected through physical examination alone (181). Therefore, besides imaging techniques in breast screening, physical examinations, which include clinical breast exams (CBE) and breast self-examination (BSE), remain vital components. However, the effectiveness of CBE and BSE in breast cancer screening is still debated, and they are not recommended as routine procedures in some guidelines (182).

CBE, conducted by healthcare professionals, involves both palpation and inspection, while BSE is performed by the patients themselves. Both aim for the early detection of tumors and overall breast health monitoring. Due to their low-risk and cost-effective nature, these examinations are particularly important in less-developed countries (183). Ongoing large cluster-randomized trials in India, comparing CBE with no breast screening, primarily indicate the benefits of CBE in early detection of breast cancer, although there is no available data yet on its impact on mortality (184,185). Previous studies that combined mammography with CBE have shown a reduction in mortality, but isolating the specific contribution of CBE is challenging (185). The effectiveness of BSE in breast cancer screening is controversial. Some studies have shown an increase in cancer detection rates, while others have not (183). There is, however, a consensus that BSE as a screening method does not reduce breast cancer mortality, as indicated by a meta-analysis (186). The increased rate of false positives should also be considered when implementing physical examinations for breast cancer screening (187).

Screening recommendations

Global status of screening

Currently, breast cancer screening programs are well-established in developed regions like Europe and the US. For example, nearly all European countries have population-based screening programs, though inequalities between them have been identified (188). In contrast, in low-income areas such as sub-Saharan Africa, no countries have established systematic screening programs, and awareness of breast cancer is poor (189). In China, large-scale screening programs were initiated in 2008, delayed by challenges such as a widely dispersed population, insufficient equipment, and a lack of insurance coverage for screening (190,191).

Regarding the temporal aspect, mortality rates in most high-income countries began decreasing in the late 1980s, partially attributed to the implementation of breast cancer screening (192), which aids in detecting advanced and metastatic cancers. It should be noted, though, that the incidence rates of later-stage breast cancer have remained stable after decades of mammography screening. Additionally, as treatments for breast cancer have improved, the impact of mammography in reducing mortality has become less significant (193). Most recently, the COVID-19 pandemic has also impacted screening programs worldwide, with overall participation rates decreasing, varying by healthcare setting (194).

Tailored screening strategies

Numerous breast cancer screening guidelines have been issued from 2010 to 2021, as summarized in a systematic review, revealing 23 different guidelines across 11 regions with varied content (154). These guidelines collectively emphasize that screening recommendations should be personalized, considering an individual's risk of developing breast cancer and their age. Additionally, race and ethnicity are also significant factors, as indicated by a recent study (195).

For women at average risk, the consensus among most guidelines is to begin screening at 40 years old. The United States Preventive Services Task Force (USPSTF) initially recommended starting at age 50 years, given the marginal net benefit of earlier screening (154). However, the latest USPSTF guidelines lower the initial age to 40 years aligning with other recommendations (196). The American Cancer Society (ACS) advises initiating screening at 45 years, while also giving women aged 40–44 years the option to participate in screening (197). Guidelines vary on the age to discontinue screening, but the decision generally considers life expectancy and comorbidity severity (198). All current guidelines agree on mammography as the primary screening tool, recommending it either annually or biennially depending on age (154).

For individuals at high risk, screening recommendations are more intensive. High-risk factors, as defined in the guidelines, include a lifetime breast cancer risk of about 20% or higher, known mutations in *BRCA1* or *BRCA2* genes, significant prior chest radiation exposure, or certain genetic syndromes (199). For these high-risk groups, screening can start as early as 30 years old and typically includes both mammography and MRI (154).

Challenges and controversies

The practice of breast cancer screening faces significant challenges, including the risks of overdiagnosis, overtreatment, and the psychological distress caused by false positives. These potential harms demand careful consideration in screening decisions. Several systematic reviews have quantified these harms. The rates of overdiagnosis vary widely, ranging from 1%–60% in clinical trials to 1%–12% in observational studies (200). An evaluation of both observed and modeled data by Bulliard *et al*. indicated that for women aged 50–69 years, overdiagnosis in screening accounts for less than 10% of invasive breast cancer cases (201). However, an increasing trend in potentially overdiagnosed breast cancer cases is observed in women aged 70 years and older. Notably, this percentage escalates to 54% in women aged 85 years and older (202).

In terms of false positives, younger age and more frequent screening are linked to a higher incidence. For women who begin annual screening at 40 years, the estimated 10-year cumulative probability of a false-positive mammography is 61%, with a biopsy rate of 7% (200,203). Other concerns, such as psychological distress (204) and radiation exposure (205,206) have been estimated in various studies, which vary widely in their methodologies.

Conclusions

This review highlights the global significance of breast cancer, emphasizing its varied incidence and mortality rates worldwide. It is important to understanding the diverse and interrelated risk factors, ranging from genetics to lifestyle. Personalized and risk-based screening strategies are essential for the early detection and effective management of breast cancer. Considering the substantial burden of breast cancer, continued global efforts are necessary for its control in the future.

Acknowledgements

This work was supported by the CAMS Innovation Fund for Medical Sciences (No. 2021-I2M-1-014 and No. 2022-I2M-2-002).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Xu H, Xu B. Breast cancer: Epidemiology, risk factors and screening. Chin J Cancer Res 2023;35(6):565-583. doi: 10.21147/j.issn.1000-9604.2023.06.02

