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REVIEW

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Advances in breast cancer screening modalities and status of global screening programs

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Abstract

Breast cancer (BC) is the most prevalent malignancy worldwide, and a continued upward trend has been predicted in the coming decades. Screening in selected targeted populations, which is effective in reducing cancer-related mortality, has been widely implemented in many countries. This review summarizes the advances in BC screening techniques, organized or opportunistic BC screening programs across different countries, and screening modalities recommended by different academic authorities. Mammography is the most widely used and effective technique for BC screening. Other complementary techniques include ultrasound, clinical breast examination, and magnetic resonance imaging. Novel screening tests, including digital breast tomosynthesis and liquid biopsies, are still under development. Globally, the implementation status of BC screening programs is uneven, which is reflected by differences in screening modes, techniques, and population coverage. The recommended optimal screening strategies varied according to the authoritative guidelines. The effectiveness of current screening programs is influenced by several factors, including low detection rate, high false-positive rate, and unsatisfactory coverage and uptake rates. Exploration of accurate BC risk prediction models and the development of risk-stratified screening strategies are highly warranted in future research.

KEYWORDS

breast cancer, guideline, mammography, screening, ultrasound

Key points

Mammography is the most widely used and most effective technique; other complementary techniques include ultrasound, clinical breast examination, and magnetic resonance imaging. Globally, the implementation status of breast cancer screening programs is uneven, which is reflected by differences in screening modes, techniques, and examination coverage. Combining effective risk prediction models and advanced screening techniques for risk-stratified screening strategies may be the future direction.

Chenyu Luo and Le Wang contributed equally to this study.

1 | INTRODUCTION

Breast cancer (BC) has surpassed lung cancer as the most prevalent cancer worldwide in 2020, with an estimated 2.3 million new cases.[1] Heterogeneous patterns of BC disease burden exist in different countries, with a significantly higher incidence in countries with a higher human development index (HDI) than that in countries with intermediate or low HDI,[1] possibly reflecting different exposure to BC-related risk factors (including lifestyle patterns, reproductive and hormonal risk factors).[2,3] In addition, many developing countries with a relatively low burden of BC have experienced remarkable upward trends in both incidence and mortality in the past decade.[4,5] Therefore, it is urgent to implement effective prevention and control strategies to reduce the global burden of BC.

Apart from primary prevention targeting modifiable risk factors, current practices have demonstrated that screening and early detection have great potential in reducing BC mortality. The underlying reason is that the survival of BC patients is strongly dependent on the stage at diagnosis, with a 99.0% 5-year relative survival rate for carcinoma in situ (CIS), while only 29.0% for patients with distant metastasis.[6] A recent meta-analysis summarizing 24 trials reported that BC screening yielded reduced BC mortality at a magnitude ranging from 12% to 20%.[7] To date, many countries have implemented population-based organized and/or opportunistic BC screening programs based on well-established screening techniques, including mammography, ultrasound, and clinical breast examination (CBE).

Understanding the current advances in BC screening is necessary to better guide BC prevention and control strategies. Several previous reviews have addressed this, but outdated data[8,9] were included, with a focus on specific districts or topics.[10] Therefore, in this review, we aimed to provide a comprehensive review of BC screening techniques, the global status of BC screening programs, and authorized BC guidelines in different countries.

2 | BC SCREENING TECHNIQUE

A few BC screening techniques are currently available and can be categorized as imaging and nonimaging techniques. Mammography is the most well-established imaging technique and other imaging techniques include ultrasound and magnetic resonance imaging (MRI). Nonimaging examinations include CBE and liquid biopsy, which are in their formative stages. A comparison of different BC screening techniques is shown in Table 1.

2.1 | Mammography

The principle of mammography is to use the physical properties of X-rays and the different densities of breast tissue to project an image of the breast onto the image receptor.[11] Currently, there are three main types of mammography available for screening: film mammography (FM), digital mammography (DM), and digital breast tomosynthesis (DBT).[12] FM is an X-ray image of the breast and has been officially recommended as a screening technique for BC by the guidelines from the National Cancer Institute of the United States since 1977.[13] X-rays produce a latent image on the film, which is visualized by the chemical processing of the film emulsion. DM uses an electronic detector to replace the conventional screen-film system and displays the images digitally on a high-resolution monitor.[14] DM has been available since 2000, which improves screening accuracy by decoupling image acquisition from the image display and optimizing them independently.[12,14] In this study, many European countries have replaced FM with DM for screening.[10] DBT is a novel technique that produces a three-dimensional (3D) image of the X-ray attenuation coefficient by obtaining a series of projection images at different angles around the breast.[8,9,15] DBT can reduce parenchymal overlap that masks cancers or creates false lesions and can potentially improve the accuracy of BC screening.[16] Compared with FM, the size of cancer detected by DBT is smaller, and the rate of negative lymph node invasion is higher.[17] A recent meta-analysis including 17 studies (1,009,790 participants) demonstrated an incremental cancer detection rate of 1.6/1000 screenings (95% confidence interval [CI]: 1.1–2.0, $p < 0.001$) and an absolute reduction in recall rate of 2.2% (95% CI: 3.0–1.4, $p < 0.001$) for DBT compared to that of two-dimensional mammography.[16] However, there is no difference between DBT and DM in interval cancer detection rate,[18–20] and research on the direct effects of DBT on BC mortality, radiation-induced cancer, and quality of life is not yet available.[21]

The latest randomized controlled trial (RCT) for the effectiveness of mammography screening was carried out in Sweden, and 133,065 women aged 40–74 years were recruited. After 29 years of follow-up, women in the mammographic screening arm had a 27% (95% CI: 11%–41%) reduction in BC mortality compared with women receiving usual care.[22] The relative risk of BC mortality for women who had undergone screening compared with that of those who had not was 0.80 (95% CI: 0.73–0.89) for the UK Independent Panel.[23] Pooled estimates from meta-analyses of RCTs (including six meta-analyses) also demonstrated that mammographic screening reduced BC mortality by at least 20%.[24]

Although mammography is an effective tool for detecting BC at an early stage, its effectiveness is affected by several host factors, including breast density,

TABLE 1 Comparison of different breast cancer screening techniques

Screening techniques	Advantages inherent to the technique	Disadvantages inherent to the technique	Categories	Advantages for screening	Disadvantages for screening
Mammography	(i) Good visualization of microcalcifications (ii) Ease to operate (iii) Inexpensive	(i) Has a certain amount of radiation	FM	Comparator	Has low sensitivity in dense breasts
			DM	Increases sensitivity and cancer detection rate slightly	Increases the recall rates
			DBT	Increases sensitivity and cancer detection rate and reduces false-positive rate	Increases the radiation dose slightly
Ultrasound	(i) Has high image resolution (ii) Noninvasive (iii) Easy to operate (iv) Inexpensive	(i) Tends to miss tiny, nonobvious masses or fat-rich breast lesions. (ii) Operator-dependent (HHUS)	HHUS ("2D")	Increases CDR in dense breasts	Has low specificity, high recall rates
			ABUS ("3D")	Increases CDR in dense breasts	Has low specificity, high biopsy rates
			Microvascular imaging and/or elastography	Increases specificity	Cannot be used as a stand-alone technique
Magnetic resonance imaging	(i) Provides 3D imaging for a more accurate display of lesions (ii) Improves CDR for lesions in dense breasts and in high and deep locations (iii) Radiation-free	(i) Has a high false-positive rate (ii) Insensitive to calcification (iii) has a long and noisy examination (iv) expensive	Noncontrast enhanced MRI (including DWI and spectroscopy)	Does not require a contrast agent May have higher sensitivity than mammography and/or DBT	Has lower sensitivity than contrast-enhanced MRI; has limited value in diffuse lesions
			Contrast-enhanced MRI	Has high sensitivity	Has low specificity, and high biopsy rates
			Abbreviated breast MRI	Has high sensitivity, shortens the duration of breast MRI examination	Reduces the specificity of breast MRI slightly
Clinical breast examination	(i) Easy to operate (ii) Inexpensive	(i) Can be affected by many host factors (age, body weight, and breast density) (ii) Operator-dependent	CBE	Plays an important role in countries where mammography screening is not feasible and/or affordable	Has low sensitivity
Liquid biopsy	(i) Can be used to assess disease progression, predict and monitor treatment response and recurrence (ii) Noninvasive	(i) Need to be further evaluated in large-scale clinical validation studies (ii) May be expensive	Liquid biopsy	Can obtain detailed tumor molecular information	Has low sensitivity and specificity Cannot be used as a stand-alone screening technique

Abbreviations: 2D, two-dimensional; 3D, three-dimensional; ABUS, automated breast ultrasonography; CBE, clinical breast examination; CDR, cancer detection rate; DBT, digital breast tomosynthesis; DM, digital mammography; DWI, diffusion-weighted imaging; FM, film mammography; HHUS, handheld ultrasonography; MRI, magnetic resonance imaging; US, ultrasound.

age, and lesion size.[12] Breast density makes the greatest impact, because of similar X-ray attenuation of dense fibroglandular tissue with tumors, in increasing the masking effect due to overlapping tissue or image artifacts and decreasing the contrast between the lesion and the surrounding tissue.[25] The sensitivity of mammography was 30%–64% for extremely dense breasts compared with 76%–98% for mainly fatty breasts.[9] Given these limitations, it is essential to explore supplemental screening tools in addition to mammography.

2.2 | Ultrasound

Breast ultrasound, which can help distinguish benign/malignant breast masses by providing a multifaceted view of the mass and detecting blood flow, is an easy-to-operate, radiation-free, and painless way to screen for BC.[26] It can be performed by using a handheld ultrasound (HHUS) unit or an automated breast ultrasound unit, which is also called 3D ultrasound.[12]

Ultrasound is typically used as a supplemental tool for further evaluation of suspicious areas or as an alternative when mammography cannot be performed.[27] This is particularly true in young women or those with dense breasts, where mammography is less effective.[28] The Japan Strategic Anticancer Randomized Trial[29] demonstrated that screening with mammography plus ultrasound in women aged 40–49 years significantly improved the cancer detection rate (5.0 per 1000 vs. 3.3 per 1000) and sensitivity (91.1%, 95% CI: 87.2%–95.0% vs. 77.0%, 95% CI: 70.3%–83.7%) than those of mammography alone. For women with dense breasts, the sensitivity of mammography alone was 74% (95% CI: 69%–79%), while the sensitivity of combined mammography and ultrasound could be 96% (95% CI: 93%–97%).[30]

Lately, mammography instruments have not been available in many low-resource settings. Ultrasound as a stand-alone screening test has been put forward, and several trials have been conducted in many countries. The American College of Radiology Imaging (ACRIN) conducted a prospective RCT of ultrasound as the primary screening option and demonstrated that the cancer detection rate with ultrasound was comparable to that of mammography.[31] However, ultrasound also has certain drawbacks, such as being less specific and having a higher biopsy rate than mammography.[9] Further, screening with manually performed HHUS is time-consuming and operator-dependent, and the consistency of reporting results from health professionals with different levels of diagnostic skills is poor.[12]

2.3 | MRI

MRI can also be used for BC screening. It has a high soft-tissue resolution and is not affected by breast density. Thus, MRI has higher sensitivity for lesions that are difficult to characterize or detect by mammography.[32,33] However, due to the high cost and long examination time, MRI is temporarily designated as a choice for women at increased risk of BC.[34] In a multicenter RCT of screening with MRI versus mammography in women with familial risk, Saadatmand et al.[35] reported that MRI was capable of detecting more cancer cases (59 per 1000 vs. 22 per 1000; $p = 0.0017$) and smaller tumors (median size, 9 mm vs. 17 mm; $p = 0.010$) than those by mammography.[35]

Abbreviated MRI is a novel technique with shorter image acquisition and interpretation times, which may increase the availability and reduce the cost of breast MRI. For instance, Kuhl et al. conducted a prospective observational study among 443 women and found that abbreviated MRI was associated with a significant reduction in image acquisition time compared to full breast MRI (3 min vs. 17 min).[36] In addition, the diagnostic accuracy of abbreviated MRI was equivalent to that of conventional MRI.[37]

2.4 | Clinical breast examination

CBE refers to breast and axillary palpation performed by the clinician on the patient, which is used in low- or middle-income countries as an alternative screening technique to mammography.[38,39] Although 5%–10% of BC cases can be detected by CBE alone, many factors affect the sensitivity of CBE, such as the clinician's experience, patients' age, and body mass index.[40] In 1998, a cluster RCT conducted in Mumbai, India, indicated that after 20 years of follow-up, biennial CBE led to a significant reduction in mortality by nearly 30% among women 50 years or older, while no significant reduction was seen in women younger than 50 years.[41] There is still controversy regarding the effectiveness of CBE as a screening tool for BC.

2.5 | Nonimaging novel screening techniques

Growing tumors actively or passively excrete debris into the bloodstream, including cell-free RNA and tumor DNA, which can be used as biomarkers for molecular-level tumor screening in the early detection of BC. Liquid biopsies help to detect tumor components in circulating blood or plasma.[42] Some preliminary studies have shown that circulating proteins,[43,44] microRNAs,[45,46] autoantibodies,[47,48] and nucleic acid methylation[49] may be promising biomarkers for early detection of BC. However, most studies are still in the exploratory phase, and clinical trial data are scarce.[50] One study showed that the sensitivity of using a combination of circulating tumor DNA and cancer-associated proteins for asymptomatic

BC was only 33%, suggesting that screening with liquid biopsy is still challenging and test methods with higher sensitivity need to be developed.[51]

3 | GLOBAL BC SCREENING PROGRAMS

BC screening is well established in Europe, the United States, Canada, Japan, the Republic of Korea, Singapore, Australia, and New Zealand. Countries in Latin America, Central and West Asia, and North Africa have few well-developed programs or have not yet implemented screening. No country in sub-Saharan Africa has developed national recommendations or guidelines for BC screening. China implemented two large pilot BC screening programs in 2008. A detailed overview of the policies and practices for BC screening programs in different countries worldwide is shown in Table 2 and the performance indicators of BC screening programs among women aged 50–69 years are shown in Table S1.

3.1 | Europe

In total, we collected data on the implementation of screening programs in 29 European countries,[10] most of which have implemented organized population-based BC screening programs, except for the Russian Federation, Bulgaria, Greece, the Czech Republic, and Slovakia (where population-based screening programs were being piloted). The target age range of women enrolled in the mammography screening program was 50–69 years in 11 of 29 countries, which was the widest target age for BC screening recommended by the European Council.[10] DM has completely replaced FM as a screening technique in 72.4% (21/29) of the countries. Seven countries also used ultrasound as a screening tool, including Finland, the Czech Republic, Austria, Belgium, Monaco, Italy, and San Marino. In the French program, CBE was used in addition to mammography.

The screening interval was 2 years in most countries except Malta and the United Kingdom (UK) (3 years). Examination coverage varied between 19.1% and 83.6% among countries, with the highest examination coverage observed in the United Kingdom and the lowest in Slovenia. A total of eight countries concentrated in Northern and Western Europe had examination coverage of over 60%, including Finland, Sweden, Norway, Denmark, the United Kingdom, Ireland, the Netherlands, and Luxemburg. Additional details are provided in Table 2.

The second report on the implementation of the Council Recommendation on Cancer Screening consolidated the current implementation and performance indicators of cancer screening programs in the European Union (EU) Member States[63] (Table S1). Of almost 15 million tests in the BC screening programs in the EU member states, the positive rate in women aged 50–69 years was 5.2% (range: 1.6%–11.8%). The average detection rate for invasive cancer was 5.2 per 1000 breasts screened, ranging from 1.8 (Portugal) to 8.1 (UK) per 1000 breasts screened, and the average detection rate for CIS was 1.0 per 1000 women screened, ranging from 0.3 (Portugal) to 2.1 (UK), with the proportion of CIS among all cancers being 16.3%, ranging from 1.2% (Poland) to 33.1% (Slovenia). Open surgery with benign results following a positive screening test, which was a rare undesirable outcome of BC screening, was 0.8 (range: 0.2–4.7) per 1000 women screened (Table S1).

3.2 | Americas

For North America, we focused on Canada[52] and the United States (US).[53] BC screening was primarily conducted through an organized population-based program in Canada, whereas it was opportunistic in the United States. In both countries, mammography was adopted as the screening technique, and the screening interval was set as 1–2 years, but the target age ranges were different; 50–69 years in Canada and 40 to >75 years in the United States. Examination coverage rates in Canada and the United States were 47.3% and 51.3%, respectively. The positive rate, CIS detection rate, and invasive cancer in Canada were 13.5%, 1.2 per 1000 women, and 4.6 per 1000 women, respectively (Table S2). However, the official data on performance indicators for the Canadian BC screening program were not updated in 2006. In addition, performance indicators are not available in the United States due to the implementation of opportunistic BC screening.

Latin America includes Central America, South America, and the Spanish-speaking countries of the Caribbean, and none of these countries meets all the criteria of the organized programs.[12] Of the 11 countries with available data, seven had a target age range for screening of 40–69 years, four used mammography as the screening technique, and five used mammography or CBE. Examination coverage in Latin America was unsatisfactory, with only four countries exceeding 30%, including Argentina, Chile, Brazil, and Uruguay. Additional details are provided in Table 2.

3.3 | Asia

Japan[54] was the first Asian country to implement a national screening program with CBE in 1987 and later introduced mammography as a screening technique. The target age for screening in Japan was 40 years or older, and the screening interval was 2 years. China designed and implemented two large pilot BC screening programs in 2008, including the Chinese National BC Screening

TABLE 2 Policies and practice for breast cancer screening programs in different countries worldwide

Countries	Year of program initiation	Type of program	Target age range	Screening method	Interval (years)	Examination coverage (%)[a]
Northern Europe[10]						
Finland	1987	PB[b]	50–69	DM, US	2	76.1
Sweden	1986	PB	NA	FM, DM	1.5–2	76.5
Norway	1995	PB	50–69	DM	2	76.6
Iceland	1987	PB	40–69	DM	2	NA
Denmark	2001	PB	50–69	DM	2	72.0
Eastern Europe						
Estonia	2002	PB	50–65	DM	2	45.9
Russian Federation	2007	NPB (pilot)	<40	DM	2	NA
Central Europe						
Poland	2006	PB	50–69	FM, DM	2	44.0
Czech Republic	2002	NPB (pilot)	45–69	DM, US	2	59.1
Slovakia	Unclear	NPB (pilot)	40+	Unclear	2	NA
Hungary	1995	PB	45–65	DM	2	38.4
Germany	2002	PB	50–69	DM	2	52.7
Austria	2014	PB	45–69	DM, US	2	36.9
Switzerland	1999	PB	50–70	FM, DM	2	44.3
Western Europe						
United Kingdom	1989	PB	50–70	DM	3	83.6
Ireland	2000	PB	50–64	DM	2	76.2
The Netherlands	1989	PB	50–75	FM, DM	2	77.5
Belgium	2000	PB	50–69	DM, US	2	33.0
Luxembourg	1992	PB	50–69	DM	2	60.4
France	1989	PB	50–74	FM, DM, CBE	2	52.3
Monaco	1994	PB	50–80	DM, US	2	NA
Southern Europe						
Greece	2004	NPB (pilot)	40–69	MM	1–2	NA
Slovenia	2008	PB	50–69	DM	2	19.1
Croatia	2006	PB	50–69	DM	2	45.1
Italy	1990	PB	50–69	FM, DM, US	2	39.1
San Marino	1993	Unclear	35–74	DM, US	2	NA
Malta	2007	PB	50–60	DM	3	NA
Spain	1990	PB	45/50–69	DM	2	59.7
Portugal	1990	PB	45–69	DM	2	33.8
North America						
Canada[52]	Unclear	PB	50–69	MM	1–2	47.3
United States[53]	Unclear	NPB (opportunistic)	40–75+	MM	1–2	51.3

(Continues)

TABLE 2 (Continued)

Countries	Year of program initiation	Type of program	Target age range	Screening method	Interval (years)	Examination coverage (%)[a]
Latin America[12]						
Argentina	Unclear	NPB	≥40	MM	2	54.2
Chile	Unclear	NPB	45–64	MM	2	36.2
Colombia	Unclear	NPB	40–69	MM	2	18.0
Mexico	Unclear	NPB	50–69	MM	2	21.0
Brazil	Unclear	NPB	40–69	MM, CBE	1–2	47.1
Dominican Republic	Unclear	NPB	40–69	MM, CBE	1	17.6
Ecuador	Unclear	NPB	40–69	MM, CBE	Unclear	10.8
Paraguay	Unclear	NPB	40–69	MM, CBE	Unclear	13.7
Uruguay	Unclear	NPB	40–69	MM, CBE	1-2	54.7
El Salvador	Unclear	NPB	40–49	MM, US	Unclear	24.3
	Unclear	NPB	15–49	BSE	Monthly	14.0
Colombia	Unclear	NPB	≥35	CBE	1	24.3
	Unclear	NPB	18–69	BSE	1	24.2
Asia						
Japan[54]	1987	PB	≥40	MM, CBE	2	18.3
China[55]	2008	NPB (pilot)	35–69 (urban)	MM, US, CBE	Unclear	54.4 (urban)
			35–59 (rural)			63.1 (rural)
Malaysia[56]	2009	NPB (opportunistic)	≥20	CBE, MM[c]	20–39 yeas: 3	51.8
					≥40 years: 1	
Republic of Korea[57]	1999	PB	≥40	MM, CBE	2	49.5
Singapore[58]	2002	PB	50–69	MM	2	NA
Vietnam[59]	2008	NPB (pilot)	Unclear	CBE	Unclear	15-20
Oceania						
Australia[60]	1991	PB	50–74	MM	2	55.0
New Zealand[61]	1999	PB	45–69	DM	2	72.0
Palau[62]	1997	PB	21–64	CBE	3	Unclear
			40–74	MM	1	Unclear

Abbreviations: BSE, breast self-examination; CBE, clinical breast examination; DM, digital mammography; FM, film mammography; MM, mammography; NA, not available; NPB, not population-based (opportunistic or pilot); PB, population-based; US, ultrasound.

[a]Examination coverage: the number of people screened with the recommended test in a given year divided by the number of people eligible for screening (the eligible target population per screening interval) in the same reference year.

[b]Population-based: in each round of screening, eligible target populations in the program's service area are individually identified and personally invited to participate in the screening.

[c]Women who are assessed as high risk are eligible for mammography screening.

Program (CNBCSP)[55] and the Chinese BC Multi-technique Independent Screening Trial (MIST),[64] using techniques including CBE, mammography, and ultrasound. In urban and rural areas, the target age ranges were 35–69 years and 35–59 years, respectively, with examination coverage rates of 54.4% and 63.1%.[55] Malaysia[56] initiated opportunistic BC screening in 2009. CBE was performed triennially for women aged 20–39 years and annually for women at average risk of 40 years or older, and women at high risk had to undergo mammography. The examination coverage rate in Malaysia was 51.8%. Korea[57] initiated population-based screening in 1999 with a target age of 40 years or older, and screening options included CBE and mammography

at a screening interval of 2 years. Singapore[58] initiated population-based screening in 2002 with a target age of 50–69 years, using mammography biennially. Vietnam[59] began pilot CBE screening in 2008, and the examination coverage rate was 15%–20%.

3.4 | Oceania

The information we obtained about the implementation of BC screening programs in Oceania is limited and presented in Table 2. Australia[60] and New Zealand[61] launched a population-based organized BC screening program in 1991 and 1999, respectively, with target age ranges of 50–74 and 45–69 years. Palau[62] initiated a population-based screening program in 1997, which included CBE screening for women aged 21–64 years and mammography screening for those aged 40–74 years.

4 | BC SCREENING GUIDELINES

The recommended guidelines for BC screening by various organizations are presented in Table S2. Each organization uses different approaches to evaluate peer-reviewed published literature and the current practices when formulating or updating guidelines, which may lead to inconsistent recommendations.[21,25,53,54,64–68]

The recommended age to initiate screening in women at average risk varies from 40 to 50 years, depending on different guidelines. Screening initiation at 40 years is recommended by the guidelines in the United States (American Cancer Society [ACS]),[53] Brazil,[66] and Japan,[54] while it is initiated at 45 years according to guidelines in Europe[21] and China.[64,68] According to the guidelines in the United States (United States Preventive Services Task Force [USPSTF]),[25] Canada,[65] and Australia,[67] the optimal age for starting BC screening is 50 years. As for women at high risk of BC, the ACS and Brazil recommend starting screening at 30 years, whereas Australia and China recommend screening at 40 years. Most guidelines recommend termination of screening at 74 years, including guidelines from the USPSTF, Canada, Europe, Australia, and Japan. Other guidelines agree to terminate screening based on life expectancy, as appropriate.

Mammography is recommended by all guidelines for women at average risk of BC. The guidelines issued by the National Cancer Center of China also recommend ultrasound as a supplemental tool. CBE is recommended for use in conjunction with mammography in Japan. The recommended screening intervals are 2 years according to the USPSTF and in Australia, 2–3 years in Canada and Europe, 1–2 years according to the ACS and in China, and 1 year in Brazil. For women at high risk, guidelines from the ACS and Brazil recommend annual screening using mammography and MRI. The Canadian guidelines recommend annual mammography and China recommends annual MRI screening or annual mammography and ultrasound screening.

5 | COST-EFFECTIVE EVALUATION FOR BC SCREENING

Several studies have shown that organized mammographic screening at biennial intervals can be cost-effective.[69–72] A study conducted by Wang et al.[73] used a microsimulation model to assess the cost-effectiveness of implementing biennial mammographic screening for women aged 45–70 years in urban China. The results showed that compared to no screening and seven other alternative scenarios, biennial mammographic screening was the most cost-effective strategy, with a discounted incremental cost-effectiveness ratio (ICER) of US$25,261 per life-year gained.

The cost-effectiveness of using ultrasound with or without CBE as a primary screening modality in low- and middle-income countries and regions remains controversial. A study investigating the expected cost-effectiveness of different strategies in Costa Rica indicated that at a coverage level of 95%, biennial CBE screening could double the life-years gained and could still be considered very cost-effective (ICER, US$5964 per disability-adjusted life year averted).[74] However, a recent study evaluating the cost-effectiveness of CBE combined with ultrasound as the primary screening modality compared with no screening in rural China found that screening was more expensive and harmed the health of rural women with an ICER of US$ –916 per quality-adjusted life-year.[75]

6 | DISCUSSION

In summary, many countries have developed BC screening guidelines and implemented screening programs. Mammography is the most widely used screening technique for women at average risk and most European countries with population-based programs have switched from FM to DM, as DM shows higher cancer detection rates and sensitivity than that of FM. Ultrasound and CBE are commonly used as supplemental tools, and MRI is used for women at increased risk of BC. Current screening strategies and published screening guidelines vary globally, as reflected by differences in screening approaches, target age ranges, and screening intervals. Biennial mammographic screening is cost-effective, but the cost-effectiveness of ultrasound with or without CBE remains controversial.

With the application of screening techniques, disadvantages, such as overdiagnosis and overtreatment, false-positive and false-negative results, and

radiation-induced cancers have emerged. The EUROSCREEN Working Group analyzed 13 observational studies from seven European countries and calculated a 6.5% (range, 1%–10%) overdiagnosis estimate.[76] Similar estimates (4%–11%) of overdiagnosis were observed in RCTs after a long follow-up period.[77,78] False-positive results are also one of the most common adverse consequences of screening. The cumulative risk of false positives from organized screening programs is estimated to be about 20% for a woman who had 10 screens between the ages of 50 and 70.[79] Less than 5% of all false-positive screens resulted in an invasive procedure.[79] False positives can have short-term negative psychological effects on some women.[80] False-negative results are another concern, such as findings that were missed in the interpretation of a screening test and rapidly growing tumors arising in the interval between two rounds of screening. Whether repeated exposure to radiation from mammography can cause BC is another issue. The US Preventive Services Task Force indicated that for every 100,000 women screened, 2–11 people might die from radiation-induced cancer.[81]

These issues make it particularly crucial to find more ideal techniques. Based on traditional breast imaging techniques, more sophisticated imaging tools have been developed, such as nuclear medicine techniques, targeted optoacoustic imaging, ultrasound transmission tomography, and molecular breast imaging.[82] For instance, nuclear medicine techniques provide functional breast imaging using specialized gamma or PET breast scanners, which supports the use of specific cellular information to assist in diagnosing BC.[82] The adoption of artificial intelligence (AI) has also shown good performance in BC imaging diagnosis. McKinney et al.[83] tested AI performance using large representative data sets from the United Kingdom and the United States and reported an absolute reduction of 5.7% and 1.2% for false positives (US and UK) and 9.4% and 2.7% for false negatives, respectively. In addition, nonimaging screening techniques, such as "liquid biopsies," may also have promising applications.[84]

It should also be recognized that there are still significant discrepancies between different countries in the implementation of BC screening. This is reflected by countries that are still committed to piloting nationwide population-based screening programs and those that cannot provide all the necessary elements of population-based screening with quality assurance. In addition, examination coverage is generally unsatisfactory even in countries where population-based screening programs have been implemented. The effectiveness of screening strategies depends not only on the performance characteristics of the screening tests but also on patient compliance. Each country or region needs to develop optimal screening programs based on local circumstances, such as disease burden, female demographic characteristics (whether predominantly young women, the proportion of women with dense breasts, genetic characteristics, etc.), exposure to risk factors, and availability of basic healthcare facilities. The successful deployment of effective screening strategies still needs to be validated in multiple RCTs in different countries.

In the precision medicine era, there is a growing need to tailor personalized screening programs based on the individual risk of BC. There are several risk assessment methods, including various risk prediction models, single-nucleotide polymorphisms (SNPs), and susceptibility genetic testing.[85] Nowadays, the polygenic risk score (PRS), which combines multiple SNPs, has been developed to achieve a more robust risk stratification capability.[86–88] Mavaddat et al.[87] validated the PRS model in 10 prospective studies and 190,040 women from the UK Biobank and indicated that compared with women in the middle quintile, those in the highest 1% of risk had 4.37- and 2.78-fold risks of developing estrogen receptor-positive and estrogen receptor-negative BC, respectively. The construction of risk prediction models that incorporate an individual genetic background, epidemiological risk factors, and imaging-related parameters may support the accurate identification of high-risk populations and the design of risk-stratified screening strategies. For instance, My Personal Breast Screening[89] is an ongoing international trial comparing personalized risk-based strategies with standard screening protocols. Individuals randomly assigned to the control arm will be screened routinely following national recommendations, while individuals in the study arm will be divided into different risk groups based on a risk model that accounts for age, family history, benign breast biopsy in the past, hormone use and reproductive history, breast density, and genotyping (PRS). This may be a new orientation for future research, and further evidence needs to be established.

7 | CONCLUSION

In summary, to further reduce the global burden of BC, continued efforts, including expanding the screening coverage of screening programs, improving the uptake rates, and developing novel screening techniques and strategies to address the limitations of current screening modalities (such as low sensitivity and false positive rates) are highly encouraged. In addition, the development of effective risk stratification models and risk-adapted screening strategies are urgently warranted to balance the cost and yield in population-based screening programs.

AUTHOR CONTRIBUTIONS

Chenyu Luo: literature review, data curation, methodology, writing—original draft preparation. **Le**

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The authors declare no conflicts of interest.

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The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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None.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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