

# BMJ Open Effectiveness of interventions for improving timely diagnosis of breast and cervical cancers in low-income and middle-income countries: a systematic review

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## ABSTRACT

**Objectives** To systematically synthesise available evidence on the nature and effectiveness of interventions for improving timely diagnosis of breast and cervical cancers in low and middle-income countries (LMICs).

**Design** A systematic review of published evidence. The review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses.

**Data sources** A comprehensive search of published literature was conducted. In addition, relevant grey literature sources and bibliographical references of included studies were searched for potentially eligible evidence.

**Study selection** Studies published between January 2010 and November 2020 were eligible for inclusion. To be eligible, studies had to report on interventions/strategies targeted at women, the general public or healthcare workers, aimed at improving the timely diagnosis of breast and/or cervical cancers in LMIC settings.

**Data extraction and synthesis** Literature search, screening, study selection, data extraction and quality appraisal were conducted by two independent reviewers. Evidence was synthesised and reported using a global taxonomy framework for early cancer diagnosis.

**Results** From the total of 10 593 records identified, 21 studies conducted across 20 LMICs were included in this review. Most of the included studies (16/21) focused primarily on interventions addressing breast cancers; two focused on cervical cancer while the rest examined multiple cancer types. Reported interventions targeted healthcare workers (12); women and adolescent girls (7) and both women and healthcare workers (3). Eight studies reported on interventions addressing access delays; seven focused on interventions addressing diagnostic delays; two reported on interventions targeted at addressing both access and diagnostic delays, and four studies assessed interventions addressing access, diagnostic and treatment delays. While most interventions were demonstrated to be feasible and effective, many of the reported outcome measures are of limited clinical relevance to diagnostic timeliness.

**Conclusions** Though limited, evidence suggests that interventions aimed at addressing barriers to timely diagnosis of breast and cervical cancer are feasible in

## Strengths and limitations of this study

- This review was designed in accordance with standard systematic review protocol guidelines.
- Literature searching was comprehensive, covering both peer-reviewed and relevant grey literature.
- No language restrictions were applied in the search.
- While most interventions were demonstrated to be feasible and effective, reported outcome measures are of limited clinical relevance to diagnostic timeliness.
- The overall strength of the synthesised evidence and applicability of findings depend on the quality of included studies.

resource-limited contexts. Future interventions need to address clinically relevant measures to better assess efficacy of interventions.

**PROSPERO registration number** CRD42020177232.

## INTRODUCTION

Breast and cervical cancers both represent a significant burden of disease globally, with a disproportionately high burden of morbidity and mortality in low and middle-income countries (LMICs).<sup>1–3</sup> The majority (53%) of new breast cancer cases occur in women living in LMICs, accounting for nearly a third of all cancers in women, and with an age-standardised incidence rate (ASIR) of 31 per 1 00 000 women in these settings.<sup>4 5</sup> Cervical cancer constitutes 16% of women's cancers in LMICs, with an ASIR of 16 per 1 00 000 women.<sup>2</sup> The increase in burdens of both cancers has been attributed to factors such as population growth, ageing societies and exposures to oncogenic risk factors.<sup>1 6</sup> While the incidence of breast and cervical cancers increases in LMICs, many cases continue to go unreported and undiagnosed; the majority

of these women present with late-stage disease, the treatment of which is often costlier and less effective.<sup>7 8</sup> These challenges have been aggravated by the COVID-19 pandemic, which immensely disrupted cancer services globally, particularly in low-resource settings.<sup>9</sup>

The timeliness of diagnosis is an important determining factor of breast and cervical cancer survival.<sup>10–13</sup> Yet, in many LMICs, breast and cervical screening and early diagnosis programmes are often opportunistic and not well organised.<sup>7 14–16</sup> One of the greatest barriers to timely cancer diagnosis in LMICs is lack of geographic access to health facilities offering screening and diagnostic services as well as the lack of well-trained care providers.<sup>6 17</sup> In addition to these, health system factors are the underlying psychosocial and cultural barriers to timely cancer help-seeking and diagnosis.<sup>6–8 18</sup> These include perceptions such as beliefs that breast cancers are contagious or punitive consequences of sins.<sup>15 19</sup>

To conceptualise and understand the pathway to cancer diagnosis, distinct events and processes from symptom awareness to diagnosis and treatment have been described. These include patients' detection of bodily changes and awareness of symptoms; decision to seek help from a healthcare provider; access to clinical evaluation, diagnosis and staging; access to treatment and follow-up.<sup>17 20–22</sup> Barriers encountered by patients in any of these phases may pose an impediment to timely cancer diagnosis and delay patients' access to care.<sup>10 23</sup> In an effort to address these barriers and provide global standards for early cancer diagnosis, the WHO published the *WHO Guide to Cancer Early Diagnosis* in 2017.<sup>24</sup> It provides an operational framework for cancer control programmes around the world to systematically address barriers that may impede timely cancer diagnosis, treatment and care. Furthermore, it specifies three essential steps of early cancer diagnosis: step 1: awareness of cancer symptoms and accessing care; step 2: clinical evaluation, diagnosis and staging and step 3: access to treatment, including pain relief. These steps were emphasised to be essential for setting cancer control priorities in the 2020 WHO Report on Cancer.<sup>25</sup>

Interventions aimed at effectively addressing barriers to timely cancer diagnosis have been studied in various settings within the different phases of the cancer care continuum.<sup>6 11</sup> It is evident that such interventions can improve the timeliness of cancer diagnosis, enable early initiation of treatment, reduce morbidity and increase the chances of survival.<sup>20 26–30</sup> However, much of this evidence is from high-income countries (HICs). Given the substantial differences between HICs and LMICs regarding health resources, environment, infrastructure, technology and medical personnel, improving time to diagnosis for breast and cervical cancer in LMIC settings may require different approaches.<sup>3</sup>

While interventions to improve the timely diagnosis of these cancers are increasingly being implemented in LMICs, there is uncertainty about their role and effectiveness. We have identified two previous reviews on this topic

within the LMIC context.<sup>6 11</sup> A scoping review by Dalton and colleagues synthesised the evidence on patient navigation strategies for cancer care in LMICs, but focused broadly on the entire cancer detection, treatment and care continuum.<sup>6</sup> A previous systematic review by Qu and colleagues assessed interventions specifically aimed at addressing barriers to timely cancer diagnosis in LMICs.<sup>11</sup> Neither specifically focused on breast and/or cervical cancer.

Therefore, the purpose of this review was to systematically synthesise the evidence on the nature and effectiveness of interventions aimed at improving timely diagnosis of symptomatic breast and cervical cancers in LMICs, by targeting the three key steps outlined by the WHO framework.<sup>24</sup> Due to the lead time and length bias associated with cancer screening programmes, this review focused on interventions targeted at improving early diagnosis of symptomatic breast and cervical cancer. Moreover, evidence demonstrates that diagnostic delays among symptomatic women are so long in LMICs.<sup>15 19</sup> Hence, interventions to reduce these delays among people with symptoms would likely have substantial impact on outcomes and are also a prerequisite for screening programmes. We sought to provide a user-friendly evidence summary for health policymakers, cancer programme managers, oncologists and cancer programme implementers, for informing further efforts to assist women in LMICs in overcoming socioeconomic, cultural and structural barriers to timely diagnosis and appropriate care, while identifying gaps for future research.

## METHODS

### Study design

This systematic review of evidence was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.<sup>31</sup> The review has been registered on the International Prospective Register of Systematic Reviews (PROSPERO).<sup>32</sup> The protocol, which was designed in accordance with the PRISMA Protocols guidelines,<sup>33</sup> has been published elsewhere.<sup>34</sup>

### Data sources

The following databases were searched: MEDLINE (via PubMed), Cochrane Library (including the Cochrane Central Register of Controlled Trials (CENTRAL) and the Database of Abstracts of Reviews of Effects (DARE)), Scopus, CINAHL, Web of Science and the International Clinical Trials Registry Platform (ICTRP). Relevant grey literature sources, including the publication database of the WHO's International Agency for Research on Cancer, the Cancer Atlas of the Union for International Cancer Control and the Global Cancer Project Map, were also searched for potentially eligible publications. The search strategy (see online supplemental appendix 1) was developed with guidance from a health science subject librarian. More details of the search strategies used are

described in the published review protocol.<sup>34</sup> Only articles published over the last 10 years (from 1 January 2010 to the date of search) were considered eligible, with no language restriction. In addition, the bibliographical references of included studies were also searched. Search was conducted from 22 June 2020 through 30 November 2020.

### Eligibility criteria

The study inclusion criteria were guided by the research question: *'What interventions targeting the key steps outlined by the WHO operational framework for early diagnosis have been used for improving timely diagnosis of symptomatic breast and cervical cancers in LMICs, and how effective are they?'*. Eligibility was determined the PICO (participants; interventions; comparator; outcomes) criteria in line with the research question. Participants included women, general public or healthcare workers (HCW) in LMICs. The definition of LMICs was based on the World Bank's current classification using per capita gross national income.<sup>35</sup> Interventions included strategies aimed at influencing the timeliness of symptomatic breast or cervical cancer diagnosis along any or a combination of the three steps of the WHO framework for early diagnosis, whether as a single focus intervention or as a multifocus intervention targeting more than one cancer type. Studies with interventions focused primarily on screening of asymptomatic individuals were excluded. Comparator was the standard of care. Outcomes were those related to any or a combination of the three steps of the WHO framework for early diagnosis, such as improved access to early diagnostic services, reduced diagnostic time and tumour downstaging. More detailed information about the eligibility criteria can be found in the published review protocol.<sup>34</sup>

### Study selection

The review consisted of two levels of screening: a title and abstract screening to identify potentially eligible publications and review of full texts to select those to be included in the review based on predefined inclusion/exclusion criteria. For the first level of screening, two reviewers (CAN and PK) independently screened the titles and abstracts of all retrieved records from the search output. Articles that were considered relevant by either or both of the reviewers were included in the full-text review. In the second step, the two reviewers (CAN and PK) independently assess the full texts to determine whether they met the inclusion/exclusion criteria. Any discordance in eligibility assessment was resolved through consensus between the two researchers, with recourse to a third arbitrator (JM) as necessary.

### Data extraction

Two reviewers (CAN and PK) independently extracted all relevant data from the included articles using a standardised data extraction tool, adapted from the framework proposed by Carlos and colleagues.<sup>36</sup> Extracted data fell under four domains: (1) study identification details

(article title, journal title, authors, country of the study, language, publication year, host institution of the study), (2) methodological characteristics (study design, study objective or research question or hypothesis, sample characteristics (eg, sample size; sex; age, ethnicity; groups and controls; follow-up duration; validation of measures; statistical analyses), (3) main findings and (4) conclusions. Study eligibility was reverified at the start of data extraction. Discrepancies in extraction were resolved through consensus. CAN combined the two spreadsheets of extracted data for analysis, and data were double checked by PK for completeness and accuracy.

### Quality assessment

Two reviewers (CAN and PK) independently assessed each included study for risk of bias, using the Cochrane risk of bias tool<sup>37</sup> for randomised clinical trials (RCT), and the Risk of Bias In Non-randomised Studies of Interventions tool<sup>38</sup> for non-randomised and observational studies. Discrepancies in study quality assessments were resolved by discussion and consensus. Further details of the quality appraisal process are discussed in the published protocol of this review.<sup>34</sup>

### Data analysis

A PRISMA flow diagram was used to illustrate the literature search results and study selection process. Outcomes were categorised according to the essential steps of early cancer diagnosis as specified in the WHO Guide to Cancer Early Diagnosis.<sup>24</sup> Plans to conduct a meta-analysis were not feasible as studies were not quantitatively comparable in terms of interventions and reported outcomes. Instead, a thematic narrative synthesis approach was used to aggregate and analyse relevant findings. Plans to assess the certainty of reviewed evidence using the Grades of Recommendation Assessment, Development and Evaluation approach<sup>39</sup> were not feasible for similar reasons. A table summarising findings from each included study was presented. JM and FMW reviewed the analysed data for accuracy and consistency with protocol.

### Patient and public involvement

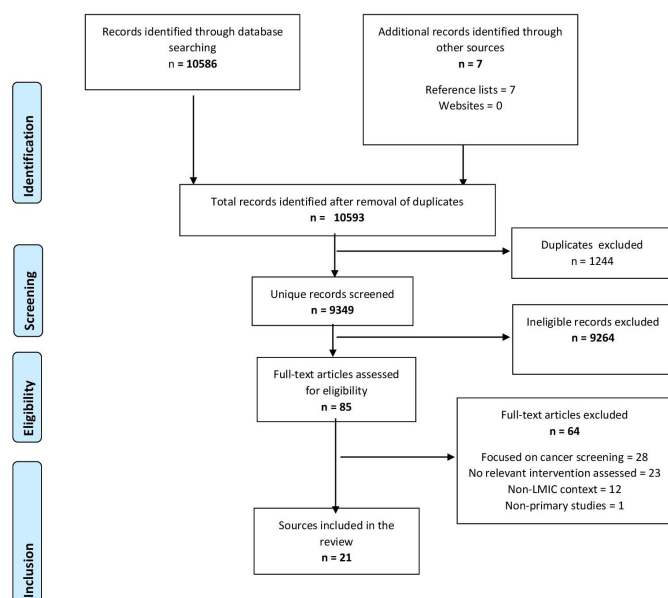
This is a review of publicly available literature. Patients and the public were not directly involved in the design, conduct, reporting or dissemination this study.

## RESULTS

### Search results

A total of 10 593 records were identified from literature database searches, from which 1244 duplicates were discarded. The remainder, 9349 unique records, had their titles and abstracts screened, from which 9264 clearly ineligible publications were excluded. The full texts of the remaining 85 potentially eligible studies were reviewed against predefined inclusion and exclusion criteria; 21 were included in the review and 64 were excluded for





**Figure 1** PRISMA flow diagram of study selection process. LMICs, low and middle-income countries; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

various reasons. **Figure 1** presents the PRISMA flow chart of the study selection process and reasons for exclusion.

### Characteristics of included studies

**Tables 1 and 2** summarise the characteristics of included studies, published between 2015 and 2020. Studies were conducted in 20 LMICs across regions of Africa (8), Europe (4), Latin America (2), Middle-East Asia (1) and South-East Asia (5). Twenty were single-country studies, in which 13 countries were represented: Bangladesh (2),<sup>8 40</sup> Botswana (2),<sup>41 42</sup> Colombia (1),<sup>43</sup> India (1),<sup>44</sup> Indonesia (1),<sup>45</sup> Iran (1),<sup>46</sup> Malaysia (2),<sup>47 48</sup> Nigeria (1),<sup>49</sup> Pakistan (1),<sup>50</sup> Rwanda (1),<sup>51</sup> South Africa (3),<sup>52–54</sup> Tanzania (1)<sup>55</sup> and Zambia (3).<sup>56–58</sup> One study had a multicountry focus, with participants recruited from nine countries: Bosnia-Herzegovina, Costa Rica, Egypt, India, North Macedonia, Pakistan, Slovenia, Turkey and Uganda.<sup>59</sup> **Figure 2** illustrates the geographical distribution of the studies.

In terms of study design, six studies were RCT,<sup>8 40 43 45 46 51</sup> six were before-and-after studies,<sup>42 44 48 49 52 54</sup> one was a longitudinal (cohort-type) observational study,<sup>55</sup> four were retrospective cohort-type studies,<sup>41 47 50 53</sup> while the remaining four were cross-sectional studies.<sup>56–59</sup>

The majority (16/21) of included studies primarily focused on interventions addressing breast cancers; two focused on cervical cancer, whereas the rest examined multiple cancer types (including breast and/or cervical cancers). Of the 21 studies, 12 targeted HCWs (including physicians, nurses, pathologists, non-physician health providers and community health workers (CHW)); 7 targeted women and adolescent girls and 3 targeted both women and HCWs. There was an even representation across urban and rural implementation contexts, with reported interventions implemented in 11 urban, 9 rural and 1 mixed (urban and rural) communities.

When categorised by the three steps of the WHO Guide to Cancer Early Diagnosis,<sup>24</sup> eight studies reported on interventions aiming to address barriers in step 1 (promoting awareness and addressing delays in access to care)<sup>8 40 44–47 49 54</sup>; another eight focused on interventions addressing step 2 (addressing diagnostic delay by optimising clinical evaluation, diagnosis and staging)<sup>42 43 50–52 55 59 60</sup>; one study reported on an intervention targeted at both steps 1 and 2<sup>53</sup>; while five studies assessed interventions targeted at all three steps (addressing access, diagnostic and treatment delays).<sup>48 56–58</sup> **Tables 1 and 2** describe the categorisation of the interventions by the three steps of the WHO Guide to Cancer Early Diagnosis.<sup>24</sup>

Only two of the included studies were determined to be of high quality (low risk of bias),<sup>43 49</sup> seven were adjudged to be of moderate quality (moderate risk of bias)<sup>8 40 45 46 51 52 57</sup> while the majority was found to be of low quality (high risk of bias).<sup>41 42 44 47 48 50 53–56 58 59</sup> **Figure 3A,B** illustrate the risk of bias assessment outcomes of the included studies.

### Interventions targeting step 1 of the WHO guide to cancer early diagnosis—promoting awareness and addressing care access delays

Interventions seeking to reduce access delays by promoting awareness, help-seeking and linkage to care were predominantly targeted at women (5),<sup>44–47 54</sup> with a few targeted at adolescent girls (1)<sup>49</sup> and community/lay health workers (2).<sup>8 40</sup>

A cluster-randomised trial assessed a self-help intervention for reducing time to diagnosis in Indonesian women with breast cancer symptoms. The intervention consisted of health education and psychoeducation using a narrative strategy, which involved the use of testimonials and storytelling.<sup>45</sup> It reduced the time between the first medical consultation and definitive diagnosis among women with breast symptoms by 13.3 days (25.90 in the intervention group vs 39.29 in the control group,  $p=0.02$ ). Another RCT by Termeh-Zonouzy evaluated the effectiveness of an educational intervention based on fear appeals using the extended parallel process model to improve attitudes, intention and timely breast cancer diagnosis in Iran. It found a significant improvement in attitude and intention ( $p=0.01$  and  $p=0.001$ , respectively), but no significant improvement was observed for early breast cancer diagnosis ( $p=0.78$ ).<sup>46</sup>

An RCT by Gadgil and colleagues investigated a programme that aimed to increase awareness on breast cancer and access to timely detection by emailing awareness brochures annually to a cohort of women in an urban occupational setting in India.<sup>44</sup> They found an increase in the proportion of women with early breast tumours and a concomitant increase in the proportion of women receiving breast conserving surgery increased postintervention when compared with the preintervention period increased from (74% to 81% and 39% to 51%, respectively). However, there were no outcomes directly related to the timeliness of the diagnoses.

**Table 1** Characteristics of included studies and categorisation of interventions according to the essential steps of the WHO Guide to Cancer Early Diagnosis (single-step interventions)

Step	Study ID	Study design	Country	Target population	Cancer type	Setting	Intervention	Primary outcome	Duration
Step 1	Gadgil <i>et al</i> <sup>44</sup>	Before-and-after study	India	Women in an occupational setting.	Breast	Urban	A programme that aimed to increase awareness on breast cancer and access to early detection by emailing awareness brochures annually to a cohort of women in an occupational setting.	Proportion of women with early tumours	3 years
	Ginsburg <i>et al</i> <sup>8</sup>	RCT	Bangladesh	CHWs	Breast	Rural	An mHealth model to increase clinic attendance for breast symptoms in rural Bangladesh: involving smart phone/applications and CHW training as part of a patient navigation programme to address potential barriers to seeking care.	Number of women with breast symptoms identified	4 months
	Ifediora and Azuike <sup>49</sup>	Before-and-after study	Nigeria	High school girls	Cervical	Rural	School-based cervical cancer prevention and early diagnosis education programme—targeting cervical cancer campaigns on teenage high schoolers in resource-limited economies.	Improvement in cervical cancer awareness and help-seeking attitude	6 months
	Chowdhury <i>et al</i> <sup>40</sup>	RCT	Bangladesh	CHWs	Breast	Rural	Population-based case finding for breast cancer by CHWs in Rural Bangladesh using different data collection methods and approaches.	Accuracy of cancer case-finding data	3 months
	Maimela <i>et al</i> <sup>54</sup>	Before-and-after study	South Africa	Women	Cervical	Urban	Decentralising colposcopy services from tertiary-level to primary-level care facility to aid early definitive diagnosis of cervical cancer.	Time to colposcopy and number of women who had colposcopy following Pap smear	6 years
	Setyowibowo <i>et al</i> <sup>45</sup>	Cluster-randomised crossover trial	Indonesia	Women	Breast	Both rural and urban	A self-help intervention for reducing time to diagnosis in women with breast cancer symptoms. It consisted of health education and psycho-education using a narrative strategy, which involved the use of testimonials and story-telling.	Time between the first medical consultation and the definitive diagnosis	3 months
	Teh <i>et al</i> <sup>47</sup>	Retrospective study	Malaysia	Women	Breast	Urban	Routine (opportunistic) screening mammogram vs targeted (high risk) screening mammogram vs diagnostic mammogram.	Proportion of women with early tumours	NA
	Termeh Zonouzy <i>et al</i> <sup>48</sup>	RCT	Iran	Women	Breast	Urban	An educational intervention based on fear appeals using the EPPM to improve attitudes, intention, and early breast cancer diagnosis.	Changes in attitude, behavioural intention towards early diagnosis	3 months

Continued

Table 1 Continued

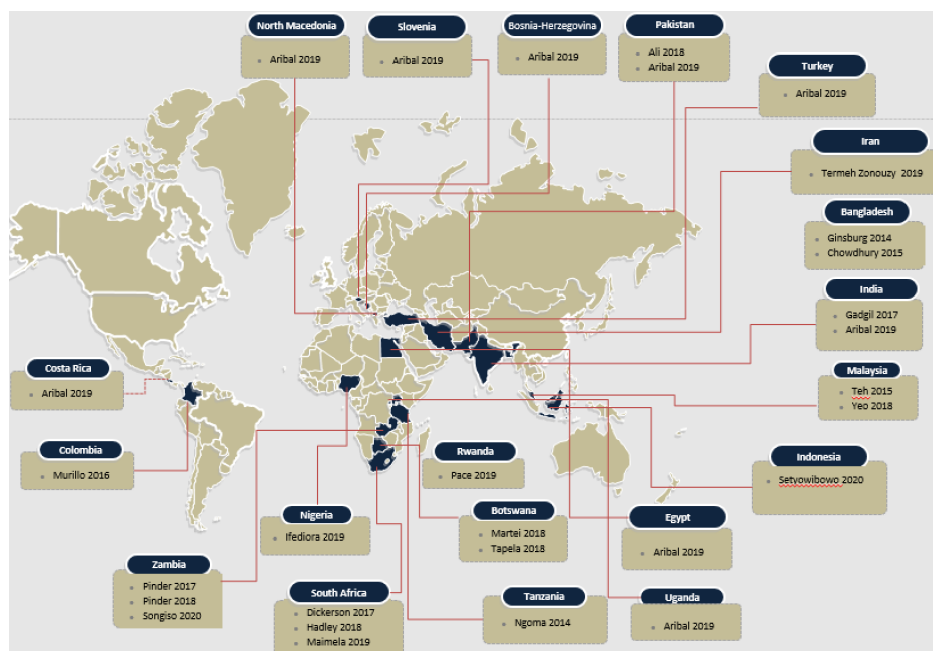
Step	Study ID	Study design	Country	Target population	Cancer type	Setting	Intervention	Primary outcome	Duration
Step 2	Ali <i>et al</i> <sup>60</sup>	Retrospective study	Pakistan	Physicians and pathologists	Multiple, including breast cancer	Urban	Adequate CI for improving TAT in surgical histopathological diagnosis.	Pathology results TAT	4 months
	Aribal <i>et al</i> <sup>69</sup>	Observational clinical study	Bosnia-Herzegovina, Costa Rica, Egypt, India, North Macedonia, Pakistan, Slovenia, Turkey, Uganda	Oncologists, radiologists, medical physicists and radiographers working on oncology centres	Breast	Urban	A programme aiming to improve early detection of breast cancer by strengthening both the clinical component and quality aspects of imaging practice of oncology centres.	Changes in mammography practice and image guided interventions	2 years
	Dickerson <i>et al</i> <sup>62</sup>	Before-and-after study	South Africa	Non-physician providers	Breast	Rural	Breast ultrasound training for non-physician providers with the goal of early diagnosis of breast cancer and downstaging in a rural setting.	Diagnostic ultrasound competence scores	3 weeks
	Martei <i>et al</i> <sup>41</sup>	Retrospective study	Botswana	Pathologists	Breast	Urban	A pathology scale-up programme to optimise breast cancer pathological diagnostic TAT in Botswana.	Breast biopsy TAT	4 years
	Murillo <i>et al</i> <sup>43</sup>	RCT	Colombia	Physicians	Breast	Urban	Opportunistic clinic-based breast cancer screening programmes to increase breast cancer screening and down-staging in Colombian women. Physicians received a 2-day training course on mammography and BIRADS grading.	Proportion of women with early tumours	2 years
	Ngoma <i>et al</i> <sup>65</sup>	Prospective cohort study	Tanzania	CHW/village navigators	Multiple, including breast and cervical	Rural	Conventional dispensary self-referral vs proactive home visits for downstaging cancer in a rural community in Tanzania.	Proportion of women with early tumours	3 years
	Tapela <i>et al</i> <sup>42</sup>	Before-and-after study	Botswana	Primary care providers	Multiple, including breast and cervical	Urban	A district-level capacity building training programme targeting primary care providers, aiming to enhance timely diagnosis of cancers.	Participants' early diagnosis competence scores	5 days

BIRADS, Breast Imaging Reporting and Data System; CHW, community health workers; CI, clinical information; EPPM, extended parallel process model; HCW, healthcare workers; NA, not applicable; NR, not reported; RCT, randomised clinical trial; TAT, turn-around time.

**Table 2** Characteristics of included studies and categorisation of interventions according to the essential steps of the WHO Guide to Cancer Early Diagnosis (multi-step interventions)

Step	Study ID	Study design	Country	Target population	Cancer type	Setting	Intervention	Primary outcome	Duration
Step 1+2	Hadley <i>et al</i> <sup>53</sup>	Retrospective/postimplementation study	South Africa	Nurses, nursing assistants and counsellor.	Breast	Rural	An improved and computerised breast cancer patient-tracking system and database as part of an ultrasound-based breast cancer early detection programme in a rural community in South Africa.	Improvement in quality of care, follow-up and clinical decision-making	NR
	Pace <i>et al</i> <sup>51</sup>	RCT	Rwanda	Health workers	Breast	Rural	It consisted of training of CHWs in how to educate community members about breast cancer symptoms recognition and early help-seeking; training of nurses in symptom recognition, CBE and appropriate referral; training of hospital-based clinicians in diagnostic breast ultrasound and ultrasound-guided core needle biopsy.	Number of breast biopsies and proportion of women with early tumours	2 years
Step 1+2+3	Songiso <i>et al</i> <sup>58</sup>	Cross-sectional study	Zambia	Women and HCWs	Breast	Urban	Establishment of a district-level breast care specialty clinic for women with breast symptoms. The clinic offers same-day breast self-awareness education, clinical breast examination, breast ultrasound, ultrasound-guided breast biopsy, surgery, referral for treatment and follow-up.	Number of single-visit breast biopsies and cytology performed	NA
	Pinder <i>et al</i> <sup>56</sup>	Cross-sectional study	Zambia	Women and HCWs in a rural setting	Breast	Rural	An algorithm that compresses the multi-step breast cancer symptom awareness, diagnostic and treatment pathway into a single visit.	Number of single-visit clinical breast examination, ultrasound, biopsy and cytology performed	NA
	Pinder <i>et al</i> <sup>57</sup>	Cross-sectional study	Zambia	Women and HCWs in a rural setting	Breast	Rural	An initiative that leverages an existing cervical cancer prevention service platform to build facility-level capacity for breast cancer care by raising awareness among women, creating a resource-appropriate breast cancer care training curricula for mid- and high-level providers, and facility-level capacity building for early detection and treatment capacity.	Number of breast biopsies performed	NA
	Yeoh <i>et al</i> <sup>48</sup>	Before-and-after study	Malaysia	Women	Breast	urban	A patient navigation programme to improve timely breast cancer diagnosis and care.	Breast biopsy TAT and proportion of women with early tumours	1 year and 1 month

CBE, clinical breast examination; CHW, community health workers; HCW, healthcare workers; RCT, randomised clinical trial; TAT, turn-around time.



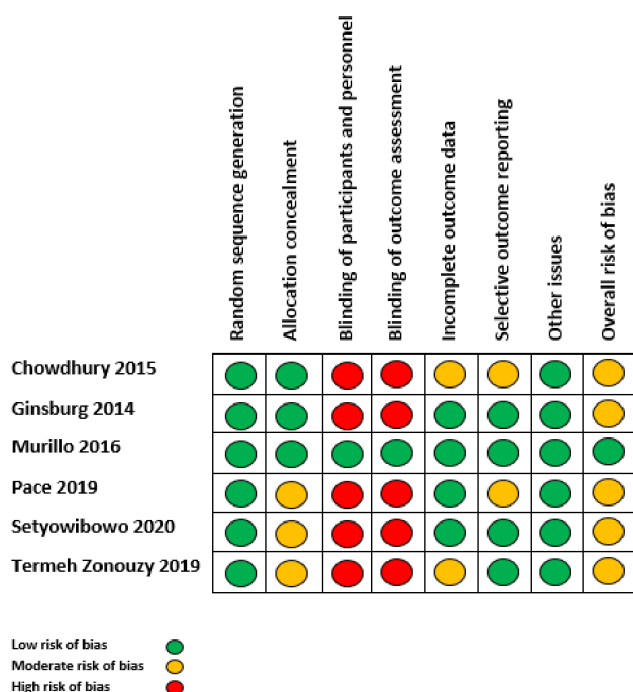
**Figure 2:** Geographical distribution of included studies (map created by authors using an open-source template sourced from <https://yourfreetemplates.com/>)

**Figure 2** Map of geographical distribution of included studies.

A before-and-after study assessed the effectiveness of decentralising colposcopy services from tertiary-level to primary-level care facility in an urban community in South Africa to aid early definitive diagnosis of cervical cancer.<sup>54</sup> The number of women who had a colposcopy at the primary healthcare facility rose threefold postdecentralisation (from 114 to 350), with an increased proportion

of women who had a colposcopy within 3 months of a Pap smear (from 11.8% to 15.4%) and reduced workload at the tertiary facility. A retrospective study compared routine (opportunistic) screening mammogram with targeted (high risk) screening mammogram and diagnostic mammogram among women in Malaysia.<sup>47</sup> It observed cancer detection rates of 0.5 %, 1.25% and 26% by opportunistic screening, targeted screening and diagnostic mammograms, respectively. The proportion of non-invasive cancer (ductal carcinoma in situ) was higher (23.1 %) in the two screening groups compared with only 2.5% in the diagnostic group, while the proportion of invasive cancer was higher in the diagnostic group. None of these outcomes was directly related to the timeliness of diagnosis.

Of the interventions targeting lay/CHW, an RCT by Ginsburg *et al* assessed the role an mHealth model that used smartphone applications and CHW training as part of a patient navigation programme to address potential barriers to seeking care in a rural community in Bangladesh.<sup>8</sup> The intervention was found to have increased clinic attendance for breast symptoms, improved data quality, higher identification of women with abnormal breast examinations and better adherence to diagnostic follow-up. Similarly, another RCT of a CHW-driven population-based case finding programme for breast cancer in a rural setting in Bangladesh found the use of mobile technology as feasible and efficient in active breast cancer case finding in rural settings. Manual data collection and reporting had missing data in 80% of cases, and took an average of 5 min longer to collect data, vs no missing data when mobile phones were used for data collection and reporting.<sup>40</sup>



**Figure 3a:** Risk of bias assessment of randomized controlled trials

**Figure 3** (A and B) Risk of bias assessment outcomes geographical distribution of the studies.



A school-based cervical cancer prevention and early diagnosis education programme targeted at rural teenage high school students Nigeria.<sup>49</sup> Notably, no significant improvements in knowledge parameters (Pap smears, risk factors and early symptoms). Nevertheless, participants who engaged more with the intervention showed significant improvements in knowledge across most parameters of knowledge.

### **Interventions targeting step 2 of the WHO guide to cancer early diagnosis—addressing diagnostic delays by optimising clinical evaluation, diagnosis and staging**

An RCT compared diagnostic outcomes between a physician-targeted opportunistic clinic-based breast cancer screening programme and usual care in an urban setting in Colombia. Physicians in the intervention clinics received a 2-day training course on breast cancer epidemiology, clinical signs and symptoms as well as the principles of mammography and Breast Imaging Reporting and Data System grading. They were instructed to perform clinical breast examination (CBE) on all eligible women, record results and refer women with suspicious findings for further diagnostic procedures. It demonstrated a higher proportion of early breast cancer diagnosed with the intervention; 68.2% of the women with breast cancer in the intervention group had breast conservation surgery, compared with 50.0% in the control group.<sup>43</sup>

A before-and-after study of a breast ultrasound training programme for non-physician providers with the goal of early diagnosis of breast cancer and downstaging in a rural setting in South Africa demonstrated improved diagnostic competencies (with pretest to post-test averages improvement of 68% in total across four competencies) (foundational knowledge, descriptive categories, benign vs malignant and lesion identification).<sup>52</sup> No outcome directly related to diagnostic timeliness was reported, however. Another before-and-after study studied district-level capacity building training programme targeting primary care providers in Botswana, aiming to enhance timely diagnosis of cancers. It found an overall performance increase (measured by the immediate impact of training on the acquisition of knowledge, attitude and skills in eight subdomains: pathophysiology, epidemiology, social context, symptoms, evaluation, treatment, documentation and follow-up) of 16.8% after participation across all subdomains.<sup>42</sup>

A prospective cohort study by Ngoma *et al* assessed the role of village navigators for case finding and showed significant downstaging of cancers in a Tanzanian village across 3 successive years ( $p < 0.001$ ).<sup>55</sup> An observational clinical study examined the effectiveness of a programme aiming to improve early detection of breast cancer by strengthening both the clinical and quality aspects of the breast imaging practice of oncology centres.<sup>59</sup> The interventions included a shift to image-guided core biopsies, implementing multidisciplinary breast meetings, implementing quality assurance procedures, transitioning to digital technologies, facilitating training activities for

relevant professionals and improving data collection processes. It was observed that the programme enhanced facility-level breast cancer early diagnostic capacity and increased number of mammography (in 7 out of 10 participating centres) and timely biopsies performed (in 8 out of 10 centres).

A retrospective study assessed the relationship between adequate clinical information (CI) and breast cancer histopathological diagnostic turnaround time (TAT) in Pakistan.<sup>50</sup> It found that breast tissue specimens with deficient CI were associated with longer TAT (>80% of the specimens took had TAT of longer than 3 days vs <50% of specimens with sufficient CI). Another retrospective study that assessed a pathology scale-up programme to optimise breast cancer pathological diagnostic TAT in Botswana found that the programme decreased median TAT for biopsy and immunohistochemistry specimens (from 21.5 days to 8 days, before and after the initiation of the programme, respectively). However, there was no significant decline in median TAT for surgical specimens.<sup>41</sup>

### **Intervention targeted at both steps 1 and 2 of the WHO guide to cancer early diagnosis—addressing access and diagnostic delays**

A cluster-randomised RCT by Pace *et al* investigated the impact of a HCW training programme on diagnosis and staging to facilitate breast cancer early diagnosis in a rural district of Rwanda.<sup>51</sup> It consisted of training of CHWs in how to educate community members about breast cancer symptoms recognition and early help seeking; training of nurses in symptom recognition, CBE and appropriate referral; training of hospital-based clinicians in diagnostic breast ultrasound and ultrasound-guided core needle biopsy. The intervention led to an increase in diagnostic health facility visits (an increase of 4.7–7.9 visits/month in intervention facilities compared with control facilities,  $p < 0.05$ ) and more breast biopsies (36.6 vs 8.9/100 000 person-years,  $p < 0.001$ ) and higher incidence of early-stage breast cancer (3.3 per 100 000 vs 0.7 per 100 000 in control areas,  $p < 0.05$ ).

Hadley and colleagues conducted a retrospective (postimplementation) study to determine the impact of an improved and computerised breast cancer patient-tracking system and database, as part of a nurse-driven and ultrasound-based breast cancer early detection programme in a rural community in South Africa.<sup>53</sup> Most health workers' involved agreed that the intervention can improve early breast cancer detection, patient follow-up, clinical decision-making, communication among clinicians. However, a majority (71%) of them reported that the system increased visit time, due to factors such as unreliable internet and inadequate computer workstations.

### **Interventions targeted at all three steps of the WHO guide to cancer early diagnosis—addressing access, diagnostic and treatment delays**

There were interventions targeting all three steps of the WHO guide. A patient navigation programme to improve

timely breast cancer diagnosis, treatment and follow-up for women in Malaysia was found to have increased the proportion of women receiving timely mammography (from 74.4% to 96.4%), biopsy (from 76.1% to 92.5%) and timely communication of diagnostic results (from 58.5% to 80.0%).<sup>48</sup> Other interventions included the establishment of a district-level breast care specialty clinic that offers same-day breast self-awareness education, clinical breast examination, breast ultrasound, ultrasound-guided breast biopsy, surgery, referral for treatment and follow-up for women with breast symptoms in Zambia<sup>58</sup>; an algorithm that compresses the multistep breast cancer symptom awareness, diagnostic and treatment pathway into a single clinic visit<sup>56</sup> and an initiative that leverages an existing cervical cancer prevention service platform to build facility-level capacity for breast cancer care by raising awareness among women, creating a resource-appropriate training curricula for mid-level and high-level providers for early detection and treatment.<sup>57</sup> Due to the cross-sectional nature of the studies reporting these interventions, they could only demonstrate the feasibility of the interventions within resource-limited contexts, and not their effectiveness.

## DISCUSSION

This systematic review highlights the diverse nature and effectiveness of interventions for the early diagnosis of symptomatic breast and cervical cancers, from 21 studies set across 20 LMICs. In spite of the limited number and methodological limitations of the studies included, this review has identified a substantial body of evidence suggesting that interventions and strategies targeting the three essential steps of the WHO operational framework for early cancer diagnosis may be feasible and effective in the context of breast and cervical cancer in LMICs. It is noteworthy that, while most of interventions were reported to be feasible and effective for improving diagnostic processes, many of their reported outcome measures are not directly related to diagnostic timeliness. Although a variety of interventions have been studied, the majority of them were targeted at improving the diagnostic capacity of HCWs (including physicians, nurses, pathologists, non-physician health providers and CHW) through training, knowledge acquisition, upskilling and better equipment.

Training interventions aimed at improving diagnostic knowledge and skills of HCWs were shown to improve diagnostic TAT<sup>41</sup> and increase detection rates<sup>43 51</sup> and downstaging.<sup>52</sup> The use of community-based patient navigation programmes driven by trained community-health or lay-health workers for breast examination, specimen collection, pathological diagnosis and follow-up was also shown to improve early diagnostic outcomes.<sup>8 40</sup> Findings are consistent with those of previous reviews.<sup>6 11</sup>

Similarly, evidence suggests that the use of health education and awareness promotion campaigns targeted at women may be effective in improving breast cancer

knowledge, attitude and help-seeking behaviour. These could include culturally sensitive and context-appropriate strategies such as a self-help intervention for reducing time to diagnosis in women with breast cancer symptoms, consisting of health education and psychoeducation through narratives, testimonials and story-telling.<sup>45</sup> Nevertheless, a school-based cervical cancer prevention and early diagnosis education programme targeting adolescent high schoolers yielded no significant improvements in the participants' overall knowledge.<sup>49</sup> This may reflect the vital influence of intervention-related and contextual factors on the effectiveness of education and awareness promotion interventions that need to be taken into account when designing such interventions.

Interventions addressing structural barriers to diagnostic services and appropriate healthcare, such as proactive home visits, patient navigation programmes and decentralisation of diagnostic services from tertiary-level to primary-level care facilities, have shown promising results in reducing diagnostic TAT and cancer downstaging.<sup>41 43 54 55</sup> While it is difficult to draw conclusions from these studies owing to their methodological limitations and potential publication bias, these findings reflect the important role of interventions targeting health system structural impediments to early cancer diagnosis in LMICs.

Evidence suggests that the use of technological interventions, such as computerised breast cancer patient-tracking systems for improving early breast cancer detection, patient follow-up and clinical decision-making, may be feasible even in rural settings.<sup>53</sup> This demonstrates the potential for the adoption and scale-up of innovative early cancer diagnosis interventions in low-resource settings. However, the effectiveness of such interventions depends largely on an adequate supply of the needed infrastructure and operational readiness, without which interventions may be ineffectiveness or counterproductive. An indication of this is the report of unreliable internet service and inadequate computer workstations as factors constraining the use of a computerised breast cancer patient-tracking system and leading to increased patient visit or consultation time.<sup>53</sup>

Our review shows a dearth of studies evaluating the effectiveness of cervical cancer early diagnosis interventions for symptomatic women, despite the substantial burden of cervical cancer and late-stage diagnosis in LMICs.<sup>1-5</sup> This trend may be as a result of the lingering stigmatisation of cervical cancer in many LMIC settings or may reflect the fact that women with cervical cancer are likely to be at an advanced stage at the time of diagnosis in such settings.<sup>61</sup> Increased investments are needed to address current cervical cancer programme evaluation and research gaps, such as through improved research funding and research capacity building; and the integration of research activities within cancer programme implementation plans. This also underscores the need for greater public health education and community awareness efforts, to mitigate existing stigma and misconceptions associated with

cervical cancer that may pose barriers to cervical cancer diagnostic service delivery and research.

The use of varied outcome measures in assessing the effectiveness of interventions across studies complicated the interpretation, aggregation and comparability of the findings. Many outcome measures reported have very limited clinical relevance to the timeliness of breast or cervical cancer diagnosis. While the most important outcome of early cancer diagnosis programmes would be to reduce cancer mortality, evaluating this outcome does require more rigorous study designs such as RCT with long follow-up periods, the cost of which may be prohibitive in low-resource settings. Hence, it is imperative for future studies in LMICs to explore the assessment of more clinically relevant proxy outcomes such as reduced time to diagnosis, improved pathology TAT and down-staging. The Anderson model, model of pathways to treatment and Aarhus statement are some of the useful tools for assessing diagnostic time-related outcomes of early cancer diagnosis interventions in standardised ways.<sup>21 22</sup>

Overall, given the rising burden of breast and cervical cancer in LMICs, the role of strategies and interventions for improving early diagnosis are relatively under-explored. While more interventions are needed, those that target both the general public and HCWs and the whole continuum of care may be more cost-effective, particularly for resource-limited settings. To enhance the feasibility and usefulness of intervention studies for generating contextually relevant evidence for improving early diagnosis, it is imperative that outcome evaluation activities are embedded as an integral component of early cancer diagnosis programmes. This can be achieved through mixed-methods implementation research strategies to evaluate and support the application of research findings into policy and practice.<sup>62</sup> It is noteworthy that the evidence included in this review relates to the period before the COVID-19 pandemic, which has disrupted essential health services, including early cancer diagnosis programmes across the world.<sup>9</sup> For this reason, it is necessary for future research to investigate the short-term and long-term impacts of the pandemic on the effectiveness of early diagnosis interventions, as movement restrictions are eased and cancer programmes return to prepandemic levels of operation.

## Limitations

Our review has some limitations worthy of note. First, most of the included studies assessed intervention outcomes using observational, non-experimental and non-standardised methods, making them prone to recall bias, selection bias, uncontrolled confounding and limited external validity. Second, as with other reviews, our study may be susceptible to publication bias in the reporting of study findings, in which positive findings have a higher likelihood of being reported. This may have been reflected in our finding of very limited evidence of non-effectiveness of interventions. Third, only a few of the studies measured intervention outcomes

beyond a duration of 1 year, hence, limiting the determination of the long-term impact of reviewed interventions. Furthermore, although we searched a wide array of literature sources, it is possible that we missed some relevant studies. Finally, our study excluded interventions that focused primarily on screening of asymptomatic individuals for reasons earlier alluded to. Hence, it is possible that some of the screening studies excluded had early diagnosis components.

## CONCLUSION

Interventions aimed at improving timely diagnosis and cancer outcomes are feasible and can be effective for improving timely diagnosis of breast and cervical cancers in resource-limited LMIC contexts. To better generate translatable evidence for improving early cancer diagnosis, our review underscores the pressing need for future studies to assess interventions using standardised methods, while reporting clinically relevant diagnostic timeliness outcomes. It is also imperative that early diagnosis interventions to adopt contextually appropriate and cost-effective approaches are well embedded within the broader health system.

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