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

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## ABSTRACT

**Introduction** Breast and cervical cancers pose a major public health burden globally, with disproportionately high incidence, morbidity and mortality in low- and middle-income countries (LMICs). The majority of women diagnosed with cancer in LMICs present with late-stage disease, the treatment of which is often costlier and less effective. While interventions to improve the timely diagnosis of these cancers are increasingly being implemented in LMICs, there is uncertainty about their role and effectiveness. The aim of this review is to systematically synthesise available evidence on the nature and effectiveness of interventions for improving timely diagnosis of breast and cervical cancers in LMICs.

**Methods and analysis** A comprehensive search of published and relevant grey literature will be conducted. The following electronic databases will be searched: MEDLINE (via PubMed), Cochrane Library, Scopus, CINAHL, Web of Science and the International Clinical Trials Registry Platform (ICTRP). Evidence will be synthesised in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA). Two reviewers will independently screen the search outputs, select studies using predefined inclusion criteria and assess each included study for risk of bias. If sufficient data are available and studies are comparable in terms of interventions and outcomes, a meta-analysis will be conducted. Where studies are not comparable and a meta-analysis is not appropriate, a narrative synthesis of findings will be reported.

**Ethics and dissemination** As this will be a systematic review of publicly available data, with no primary data collection, it will not require ethical approval. Findings will be disseminated widely through a peer-reviewed publication and forums such as conferences, workshops and community engagement sessions. This review will provide a user-friendly evidence summary for informing further efforts at developing and implementing interventions for addressing delays in breast and cervical cancer diagnosis in LMICs.

**PROSPERO registration number** CRD42020177232.

## Strengths and limitations of this study

- This protocol was designed in accordance with standard systematic review protocol guidelines.
- Literature search will be comprehensive, covering both peer-reviewed and relevant grey literature.
- No language restriction will be applied in the search.
- It is possible that the review will not include all relevant literature available, as some may not be accessible at the time of review.
- The overall strength and applicability of the synthesised evidence will depend on the quality of included studies.

## INTRODUCTION

Breast and cervical cancer constitute a major public health burden globally.[1 2] They are particularly burdensome in low- and middle-income countries (LMICs), where their incidence, morbidity and mortality are disproportionately high.[2 3] Breast cancer, the the most common cancer among women worldwide, accounts for about 30% of all cancers in women in LMICs.[4] The majority (53%) of new breast cancer cases occur in women living in LMICs.[5] With an age-standardised incidence rate (ASIR) of 31 per 100 000 women, there are over half a million new cases every year in LMICs.[4] Cervical cancer represents 16% of the total cancer burden in LMICs, with an ASIR of 16 per 100 000 women and an incidence of 300 000 new cases every year.[2] Nine out of every 10 of these cases will likely lead to premature death.[2]

Nearly 70% of all cancer deaths, including those due to breast and cervical cancer, occur in LMICs.[4] Of greater concern is that the number of new cancer cases, their associated morbidity and deaths in LMICs are expected to grow substantially in the

coming decades.[6] This growth will be due in part to population growth, shifts in demographics and exposures to known risk factors, in keeping with the epidemiological transition from communicable diseases to non-communicable diseases.[1 6] While the incidence of cancers increases in LMICs, many cases continue to go undiagnosed because of a lack of high-quality population-based registries, and when diagnosed, the majority present at late-stage with consequently poor outcomes.[7–9]

Breast and cervical cancer mortality and survival are largely influenced by the timeliness of diagnosis and effectiveness of treatment modalities.[7 8 10] In many LMICs, breast and cervical screening and early diagnosis programmes do exist in some form, however, they tend to be opportunistic and not well organised.[11–13] There is often poor access to high quality, affordable breast and cervical cancer treatment, particularly where the health systems are fragile or fragmented.[6 14] In addition to these health system factors are the underlying sociocultural and financial barriers to cancer prevention, diagnosis and treatment services.[6 12 15 16] Lay beliefs, such as beliefs that breast cancers are punitive consequences of sins or a type of divine retribution, are held within some communities in LMICs, as are concerns that breast cancer surgery may result in deformity, which may subsequently lead to divorce or family abandonment.[13 17] As a result of these issues, women in LMICs with breast and cervical cancers may be reluctant to seek care following their awareness of symptoms, leading to delays in diagnosis. Consequently, a high proportion of patients are diagnosed at advanced stage, when treatment is often less effective and more expensive.[12 15]

Evidence suggests that improved timeliness of cancer diagnosis is critical for optimising patients' navigation of the pathway from symptom awareness to treatment and follow-up.[18–20] Timely cancer diagnosis can enhance opportunities for treatment with curative intent.[21] However, much of this evidence is from high-income countries (HICs), many of which do not have the sociocultural, financial, health system and knowledge barriers to timely cancer diagnosis and effective cancer treatment that many LMICs grapple with.[6 8] In an effort to address this evidence gap and provide global standards for early cancer diagnosis, the WHO published the *WHO Guide to Cancer Early Diagnosis* in 2017.[22] The guide provides a clear framework for cancer control programmes around the world to systematically address barriers that may impede timely cancer diagnosis, treatment and care. More recently, the 2020 WHO report on cancer specifies three steps of early cancer diagnosis: awareness of symptoms, rapid clinical and pathological diagnosis and referral to an appropriate treating facility.[23]

The distinct phases of cancer patients' pathways from symptom awareness to diagnosis and treatment have been described. They include patients' awareness of symptoms; access to clinical evaluation, diagnosis and staging; access to treatment; and follow-up.[14 18] The phases are conceptualised based on the Model of Pathways to Treatment framework proposed by Walter, Scott and colleagues, which identifies five key events in the pathway to care: detection of bodily changes; perceived reasons to discuss symptoms with a healthcare provider; first consultation with a healthcare provider; diagnosis and start of treatment.[24 25] The framework also identifies four important intervals between these phases: the appraisal, help seeking, diagnostic and the pre-treatment intervals. These events and processes represent particular moments at which barriers may exist and delay patients' access to care before or after a cancer diagnosis.[7 26]

## STUDY RATIONALE

Interventions aimed at promoting early breast and cervical cancer detection are increasingly being adopted globally, particularly in HICs.[21 27 28] 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.[3] We have identified two previous reviews on this topic within the LMIC context.[6 8] A scoping review by Dalton and colleagues synthesised the evidence on patient navigation strategies for cancer care in LMICs, but focussed broadly on the entire cancer detection, treatment and care continuum, and not specific to breast or cervical cancer.[6] The literature search was concluded in December 2018. A systematic review by Qu and colleagues assessed interventions specifically aimed at addressing barriers to early cancer diagnosis in LMICs.[8] However, it did not specifically focus on breast and cervical cancer, and the literature search was concluded in November 2017.

Therefore, our review aims to provide a more up to date, robust and comprehensive synthesis of the evidence on the nature and effectiveness of interventions for improving timely diagnosis of breast and cervical cancer in LMICs. We have focussed on early diagnosis of symptomatic breast and cervical cancers, as the outcome (such as clinical downstaging) is easier to evaluate, unlike screening in which outcomes may be complicated by factors such as the time lag between cervical cancer screening and symptom development, as well as over-diagnosis of precancerous cervical lesions that may not have become symptomatic nor pose a serious health threat even without intervention. Overall, the review seeks to provide a user-friendly evidence summary for health policymakers, cancer programme managers, oncologists and early cancer diagnosis programme implementers, for informing further efforts at addressing breast and cervical cancer diagnostic delays in LMICs, while identifying gaps for future research.

## METHODS AND ANALYSIS

### Study design

The protocol is designed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines.[29] The review has been registered on the International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD42020177232).[30]

### Search strategy

The search strategy will be developed with guidance from a health sciences subject librarian, in accordance with the Cochrane highly sensitive search guidelines.[31] The search strategy will be pre-tested prior to the actual search.

Search terms and free-text words will be combined using the Boolean operators 'AND' and 'OR', such as (breast OR cervical OR cervix, cancer OR neoplasm OR malignancy OR tumours) AND (diagnosis OR diagnostic OR screening OR detection OR discovery) AND (early OR timely OR time OR late OR delay) AND (efficacy OR effectiveness OR improvement). In order to restrict search to LMICs, a filter containing all LMICs countries, regional blocs and other common categorisations will be added. See online supplemental appendix 1 for provisional search strategy.

A comprehensive literature search will be conducted on the following electronic databases: 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). The literature search will be guided by the research question using the Population, Intervention, Comparison, Outcome and Study design (PICO) strategy.[32] Search terms will include the use of controlled descriptors (such as MedicalSubject Headings terms, CINAHL and headings) and their synonyms. Additionally, relevant grey literature will be searched for potentially eligible articles, including the publication database of the WHO's International Agency for Research on Cancer (IARC), the Cancer Atlas of the Union for International Cancer Control (UICC) and the Global Cancer Project Map. A hand-search of reference lists of included studies and grey literature sources will be conducted to identify additional published and grey literature. For recency, only articles published over the last 10 years (from 2010 to date) will be considered eligible. No language restrictions will be applied, and any potentially eligible article in a language other than English will be translated using a web-based translation tool.[33] The preliminary literature search was initiated on 22 June 2020.

### Study selection

The study inclusion criteria will be guided by the research question: 'What interventions have been used for improving timely diagnosis of breast and cervical cancers in LMICs, and how effective are they?'. Our PICO criteria in line with the research question are outlined below:

Eligible studies will have to report on early diagnosis strategies for breast and cervical cancers targeting women, the general public or healthcare workers in LMICs. The definition of LMICs will be based on the World Bank's current classification using per capita gross national income.[34] Multinational literature involving LMIC and non-LMIC countries and meeting inclusion criteria will be included, except where country-specific information cannot be abstracted.

Included articles will be required to involve an intervention or implemented strategy that aimed to influence the timeliness of breast or cervical cancer diagnosis, whether as a single focus intervention or as multi-focus intervention targeting more than one cancer type. Studies focussed solely or mainly on the theoretical or conceptual knowledge, attitude and perception of the timeliness of breast or cervical cancer diagnosis without assessing intervention outcomes will be excluded, as will those reporting outcomes there are not related to diagnostic timeliness. Studies with interventions focussed primarily on screening of asymptomatic individuals will also be excluded.

Where applicable, articles that compared between reported interventions and usual standard of practice (without intervention) will be included. Studies that compared multiple interventions (such as those targeting different populations such as cancer patients, healthcare workers or communities) will also be considered. Therefore, study design eligibility will include randomised trials, non-randomised trials and observational studies, with or without controls. However, inclusion will be limited to primary studies, while systematic and scoping reviews will be excluded.

Intervention outcomes will not be limited to any particular type, in order to capture as many relevant studies as possible. These may include improvements in knowledge, stage of disease at presentation, reduction in delay from symptom awareness to diagnosis, time from health facility presentation to definitive diagnosis or time interval from receipt of specimen to pathology reporting of final diagnosis. Outcomes will be classified according to the essential steps of early cancer diagnosis as specified in the WHO Guide to Cancer Early Diagnosis.[22]

### Screening and data extraction

The review process will consist 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) will independently screen the titles and abstracts of all retrieved records from the search output. Articles that are considered relevant by either or both of the reviewers will be included in the full-text review. Following the removal of duplicates, full texts of remaining studies will be retrieved. In the second step,

the two reviewers will then independently assess the full texts to determine if they meet the inclusion/exclusion criteria. Any discordance in their eligibility assessment will be resolved through consensus between the two researchers. Any further disagreements will be resolved by a third reviewer (JM).

Two reviewers (CAN and PK) will independently extract and record all relevant data from the included articles using a standardised data extraction tool, adapted from the framework proposed by Carlos and colleagues.[35] The tool includes 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 will be re-verified at the start of/during data extraction.

Where the relevant outcome data in the original article are unclear or missing, the corresponding author will be contacted via email for clarification. Any disagreements between the two reviewers will be resolved by discussion, and if a consensus is not reached, a third reviewer (JM) will arbitrate. The first reviewer (CAN) will combine the two spreadsheets of extracted data for analysis. PK will double-check the entered data for completeness and verify the accuracy of analysis. JM and FMW will review analysed data for accuracy and consistency with protocol.

### Study quality assessment

Two reviewers (CAN and PK) will independently assess each included study for risk of bias; again, disagreements will be resolved by a third reviewer (JM). For randomised trials, the five domains of the Cochrane risk of bias tool will be used.[36] These five domains include: the randomisation process (random sequence generation and allocation concealment), deviations from intended interventions (blinding of participants and personnel), measurement of the outcome (blinding of outcome assessment), incomplete outcome or missing data and selective outcome reporting. For each included study, the two reviewers will independently describe and make judgement of 'Low risk' of bias, 'High risk' of bias or 'Some risk' of bias accordingly.

For non-randomised and observational studies, the Risk of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool will be used for assessing methodological quality.[37] The tool covers seven distinct domains: confounding; selection; intervention classification; deviations from intended interventions; missing data; measurement of outcomes and selection of reported results. Overall, risks of bias judgements are categorised as 'Low risk', 'Moderate risk', 'Serious risk' and 'Critical risk' of bias, with 'Low risk' corresponding to the risk of bias in a high quality randomised trial. Both reviewers' independent risk of bias assessments will be compared, and any discrepancies will be resolved by discussion and consensus. The risk of bias for each outcome across individual studies will be summarised as a narrative statement, and supported by a risk of bias table presenting domain-specific judgements.

### Descriptive analysis and meta-analysis

A narrative synthesis of all relevant findings from the included studies will be reported in accordance with the PRISMA statement.[38] A PRISMA flow diagram will be used to illustrate the literature search results and study selection process (see online supplemental appendix 2). If sufficient data are available and studies are comparable in terms of interventions and outcomes, a meta-analysis will also be conducted. In case of moderate-to-high heterogeneity between studies ($I^2$ statistic >25%), estimates will be pooled using random effect meta-analysis models, otherwise fixed effect models will be used.[39] A fixed effect meta-analysis assumes all studies are estimating the same (fixed) treatment effect, whereas a random effects meta-analysis allows for differences in the treatment effect across studies.[40] Where studies are not comparable and a meta-analysis is not feasible, only a narrative report of findings will be presented. The meta-analysis will present outcomes as risk ratios with their corresponding 95% CIs for dichotomous data, and standardised mean differences (SMD) with their corresponding 95% CIs for continuous data. The SMD will be categorised as small, medium and large based on the thresholds 0.2, 0.5 and 0.8, respectively, as proposed by Cohen.[41] The 95% CI will be used to represent the deviation from the point estimate for both the individual studies and the pooled estimate.

Heterogeneity between the studies will be assessed using Forest plots visually, as well as statistically using the $\chi^2$ test of homogeneity (with significance defined at the 10% $\alpha$-level and quantified with the Higgins' $I^2$ statistic).[39 42] Funnel plots of estimated differences in outcome effects against their SEs will be used to assess the presence of publication bias. Publication bias is defined as the tendency of authors to publish studies with significant results.[43] This will be assessed if at least 10 studies are included in the meta-analysis.[42] Subgroup analyses will be conducted, with subgroups defined by study design, cancer site, type of intervention and region/continent.

Sensitivity analyses will be performed to assess the effect of risk of bias on pooled estimates, and to investigate the robustness of the pooled estimates (ie, by including and excluding studies with high risk of bias and/or those that did not use validated outcome measurement tools).

The Grades of Recommendation Assessment, Development and Evaluation (GRADE) approach will be employed to assess the certainty of the evidence on the effectiveness of reported interventions.[44] This critical appraisal of the certainty of each evidence will be useful for dealing with, and interpreting conflicting findings. A table summarising findings from each included study will be presented. Meta-analysis will be performed with the Review Manager 5.3 (RevMan) review software.[45]

## Patient and public involvement

As this will be a review of publicly available literature, patients and the public were not directly involved in the design of this protocol.

## Ethics and dissemination

This will be a systematic review of publicly available literature, with no primary data collection. Hence, it will not require ethical approval. Findings will be disseminated widely through peer-reviewed publication and in various media, for example, conferences, congresses or symposia: This review will provide a user-friendly evidence summary for health policymakers, cancer programme managers and frontline health workers, for informing further efforts at addressing breast and cervical cancer diagnostic delays in LMICs, while identifying opportunities for future research.

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