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Cost Effectiveness of Screening & Diagnostic Methods for Cervical Cancer in Women aged 30-65 Years Globally: A Systematic Review Protocol to Guide Policy Documents

Diksha LNU[1], Sheilja Walia[2], Hariom Sharma[3], Preethu Prasannakumar[4], Musarrat Siddiqui[5], Ashu Ranga[6], Palak Dhiman[7], Neelam Tirkey[8], Kushagr Duggal[9], Tahseen Kulsum[10], Ashutosh Kothari[11], Aashima Bhatnagar[12], Himanshu Bhushan[13]

[1,3,4,5,6,7,8,11]Consultant, Public Health Administration Division, National Health Systems Resource Centre
[2]Fellow, Public Health Administration Division, National Health Systems Resource Centre
[9]Consultant, Surveillance, Share India, CDC
[10]Junior Consultant, Surveillance, SHARE India, CDC
[12]Senior Consultant, Public Health Administration Division, National Health Systems Resource Centre
[13]Former Advisor, Public Health Administration Division, National Health Systems Resource Centre

Abstract

Background: Cervical canceris the fourth most common cancer in females, with high prevalence in developing countries, and the most common cause (99%) is the Human Papillomavirus (HPV). The global incidence of cervical cancer is increasing every year, with an incidence of 13.3 cases per 100,000 women and a mortality rate of 7.2 deaths per 100,000 women in 2020. There are various screening and diagnostic methods; however, the availability of any strong evidence on the most cost-effective method is limited. This review systematically analyzes the available screening and diagnostic methodologies for cervical cancer, sensitivity, specificity, and cost implications.

Methods and Analysis: Electronic databases like PubMed, Cochrane, and Google Scholar willbe systematically searched for relevant articles using medical subject headings (MeSH) terms. Eight reviewers (DL, SW, PP, AK, AR, MS, TK, NT) will independently assess titles and abstracts against the selection criteria during the first phase. Five reviewers will assess all full-text papers before the final decision is made. The studies will be selected based on the predefinedinclusion and exclusion criteria. The selected systematic reviews will undergo a quality assessment using the PRISMA checklist and RCTs using CONSORT and CHEERS statements to examine economic evaluations. A narrative synthesis will be formulated from the studies based on two types of outcomes- Clinical and Economical. If sufficient data is available, a meta-analysis will be performed.

Conclusion: The results from this study may aid in identifying factors influencing test performance and have evidence of the cost-effectiveness of the screening and diagnostic tests for cervical cancer. This review will generate a platform for more studies that will provide answers to crucial research concerns about cervical cancer screening.

Ethics & Dissemination: This review is based on the already published literature and secondary data, so ethical approval does not apply to this study. We will publish our findings in a peer-reviewed journal and develop accessible summaries.

Keywords: Cervical Cancer, Cost-effectiveness, Economic evaluations, Screening.

Background

Cervical cancer is an emerging global public health issue having high incidence and mortality rates if not detected early.Earlyscreening and detection helpsignificantly reduce mortality as it's a curable disease in the early stages. Globally, it is the fourth most common cancer in females, with high prevalence in developing, low- and middle-income countries (LMICs). Human Papilloma Virus (HPV) is the most common cause (99%) of cervical cancer, among other causes. Among the population infected, most population (nearly 90%) clears the infection eventually[1]. HPV 16 and HPV 18 are the commonest strains (nearly 70%) found in most cervical pre-cancers[2]. Predisposing factors for HPV infection are early onset of sexual intercourse, HPV genome, multiple sexual partners, immuno- compromised status, smoking, and oral contraceptive pills. HPV is mainly transmitted through sexual contact, and disease development takes 10-20 years after exposure. Apart from HPV, some studies show that HIV-positive females are more prone to developing cervical cancer than non-HIV-positive females[3].

The global incidence of cervical cancer is increasing every year. In 2020, it was estimated to have nearly 604,000 new cases and approximately 342,000 deaths, with anage-standardized incidence of 13.3 cases per 100,000 women years and a mortality rate of 7.2 deaths per 100,000 women years [4]. As reported in the Lancet, 69% of all countries recommend cervical cancer screening. Cytology is the primary screening test in 78% of the countries, while 35% recommend primary HPV-based screening. Visual inspection with acetic acid was the most recommended test in resource-limited settings[5].

In 2021, India reported 123907 new cervical cancer cases, 77348 deaths and a crude cervical cancer incidence rate of (18.7)[6]. The age-adjustedincidence rate of cervical cancer is highest in Mizoram (23.07)[7]. Among the districts, Papum-Pare of Arunachal Pradesh is the most affected district, with an incidence rate of (27.7). In 2020, World Health Assembly adopted the global strategy for cervical cancer elimination that aimed to reduce the incidence rate below 4 per one lakh women. The WHO has established the 90-70-90 targets to be achieved by 2030 and to be maintained to cross this threshold by the end of the twenty-first century with the target that 90% of girls are fully protected against HPV by the age of 15; 70% of women are subjected to high-performance screening by the ages of 35 and 45; 90% of women who are diagnosed with cervical illness undergo treatment, and 90% of women with precancer are also treated.

Methods used for Cervical cancer screening are Visual Pelvic examination, PAP (Papanicolaou) smear and HPV (Human Papilloma Virus) DNA testing. Visual Inspection (Pelvic examination) has shown variable accuracy as it requires intensive training of professionals. Visual Inspection with Acetic Acid (VIA), Visual inspection through magnification (VIAM), and Visual Inspection through Lugol's Iodine (VILI) are some of the visual inspections done for cervical cancer screening[8]. A pap smear is done by collecting a sample from the cervix and then preparing a smear observed under the microscope (cytology) for any cancer or abnormal precancerous cells. In some earlier studies, higher sensitivity was found in VIA compared to VIAM and cytology, whereas pap smears had high specificity. The PAP smear was a sensitive (94%) and specific (81.4%) method in detecting precancerous lesions of the cervix as found in tertiary care hospitals[9].

HPV sample collection is also done through the same technique as a Pap smear for examining the HPV virus in the cells. HPV DNA detection has high sensitivity than HPV mRNA, but conversely, HPV m RNA has high specificity than HPV DNA. WHO also recommends HPV DNA detection as the primary screening methodfor cervical cancer[10]. However, these tests have low specificity for cervical precancer,especially in populations with a high prevalence of HPV. For diagnostic purposes, colposcopy, histopathological examination (conization or cervical biopsy) or radiological investigations (Chest radiographs, intravenous pyelography, and barium enema), and endoscopy (cystoscopy or sigmoidoscopy) are done[11]. CT, MRI, and PET scans are often used to see the extent of the disease (metastasis or nearby tissue proliferation lesions).

The National Cancer Control Program was started in the year 1975 for the strengthening of premier cancer hospitals/ Institutions in India. In 1984, the strategy shifted to primary prevention and early screening of cervical cancer[12]. In 1990-91, the District Cancer Control program started in selected districts, and since then, many revisions and additions have been made to NCCP[13]. The program focused more on risk reduction and opportunistic screening or screening through camps for women over 30 years. In 2010, the Government of India launched the National Program for Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS). Under NPCDCS, the Government of India has introduced population-based cervical cancer screening in 100 districts of India on a pilot basis[14].

However, implementing a national-level screening program for cervical cancer is arduous due to resource constraints like limited infrastructure and a trained workforce. Various screening and diagnostic methods for cervical cancer are being used globally; however, strong evidence on the most cost-effective method that can be used in a low-resource setting is limited.

This review systematically analyzes the present-day screening and diagnostic methodologies for cervical cancer, sensitivity and specificity and their cost implications. The results may lead to cost-effective methods which can be applied in low-resource settings and Low middle-income countries for mass screening of cervical cancer in the population. Early screening of cervical cancer will eventually lead to a reduction in cervical cancer cases, a proportional decrease in treatment costs, a reduction of out-of-pocket expenditure, and reduced morbidity and mortality from cervical cancer.

Methods/ Designs

Review Questions

1. What is the most cost-effective screening method for cervical cancer in women aged 30-65 years globally?
2. What is the most cost-effective diagnostic method for cervical cancer in women aged 30-65 years globally?

Objectives

The primary objective of this study is to systematically review and analyze the cost-effectiveness of various screening and diagnostic methods used for cervical cancer across the globe. This review will evaluate the limitations, costings, sensitivity, specificity, easy availability, and effectiveness of these screening and diagnostic methods across community and healthcare facility settings.

The secondary objective of this review is to determine how the methods (in terms of costs included outcomes and method of assessing cost-effectiveness) vary by setting, country, screening & diagnostic methods, test preferencesand period of the study regarding the respective guidelines available from the country where the study was conducted.

The guidelines by the Cochrane Collaboration for Reviews and Centre for Reviews and Dissemination (CRD)[15] will be followed and reported according to the PRISMA-P guidelines[16].

Eligibility criteria

Since the objective of the systematic review is to evaluate the cost-effectiveness of various screening and diagnostic methods used for cervical cancer. So, the studies included in the review will be based on the following inclusion criteria: -

Sr. No	Indicators	Inclusion Criteria	Exclusion Criteria
1	**Types of studies**	Full economic evaluations (studies in which both the costs and outcomes of the alternative methods/tests for screening and diagnostic are examined, analyzed and in which a comparison of two or more methods/tests is undertaken) including Trial-based, Non-trial based, Decision model and Trial-based model studies, Government policy documents & reports and other government publications through websites and registries on cervical cancer.	Qualitative studies, conference abstracts, comments, editorials and study protocols will be excluded; partial economic evaluations will be excluded because the review will synthesize the evidence base for cost- the effectiveness of screening & diagnostic methods for cervical cancer.

Sr. No	Indicators	Inclusion Criteria	Exclusion Criteria
2	**Time Duration**	Articles Published from January 1, 1990, to January 1, 2023.	Articles published before January 1, 1990, or after January 1, 2023.
3	**Domain being studied**	Screening and diagnostic methods used for cervical cancer.	Studies not including the domain:- screening & diagnostic methods used for cervical cancer.
4	**Participants/ Population**	Adult females aged 30-65 years for cervical cancer screening and all females diagnosed with cervical cancer will be included. Community-based and healthcare facility-based screening and diagnostic methods/tests will be included, and the target population will be adult females all over the globe.	Other than inclusion criteria.
5	**Intervention(s) and exposure (s)**	Any screening method/test for early detection of cervical cancer for primary prevention and definitive diagnostic tests used all over the globe will be included.	Other than inclusion criteria.
7	**Comparator(s) /control**	There will be no restrictions on the comparator(s) types. For example, the comparator will be another screening method and diagnostic test. However, the study will have a clear definition of the comparison.	Other than inclusion criteria.
8	**Outcome(s)**	In outcomes, the sensitivity and specificity of screening & diagnostic method/test will be included for review. Further, the costing details and outcomes regarding ICER will	Other than inclusion criteria.

Sr. No	Indicators	Inclusion Criteria	Exclusion Criteria
		be analyzed.	
9	Other criteria	Articles published in the English language will only be included in this review.	

Information sources & portals

PubMed, MEDLINE, Embase, Google Scholar, Cochrane Central Register of Controlled Trials (CENTRAL), and Cochrane Database of Systematic Reviews will be searched. In addition, the following sources will be used to find potential new studies, including sources for reviewing grey literature, tracking citations in Google Scholar to find more references, and routinely looking through the references in relevant studies and review articles.

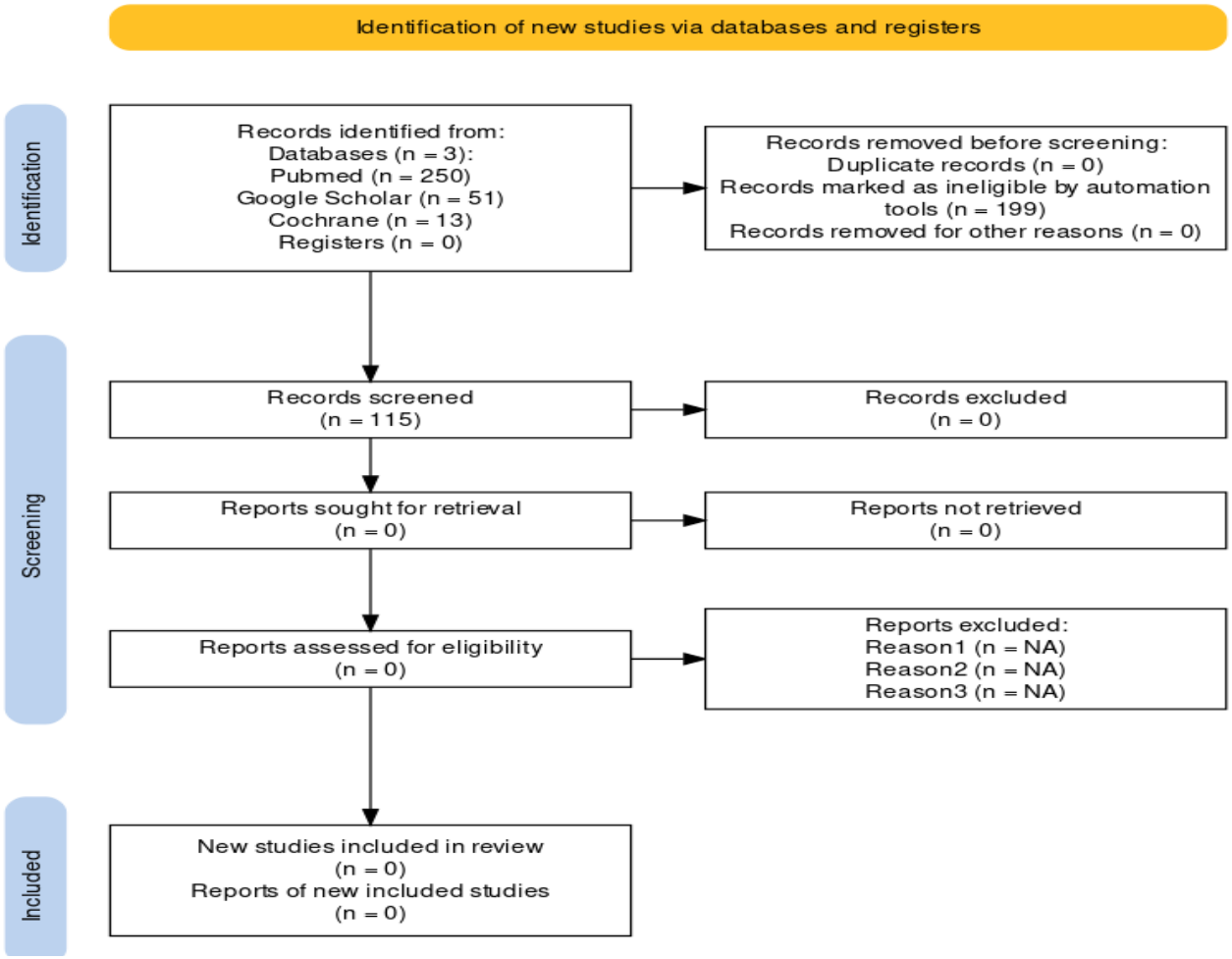
Potential Search Terms

The following terms will be used as search terms: systematic review, economic evaluation, cost-effectiveness, cost estimation, cervical cancer, screening methods, screening tests, adult females, and diagnostic tests. The search strategy for PubMed and MEDLINE will bebased on medical subject headings (MeSH) terms and text words from key papers related to the condition. The search terms and text words will also be adapted for use in other bibliographic databases.

Study selection procedure

The review will use a two-phase methodology, and the inclusion and exclusion criteria will be used to determine which studies to include. Eightreviewers (DL, SW,PP, AK, AR, MS, TK, NT) will independently assess titles and abstracts against the selection criteria during the first phase. In addition, the full-text version will be requested if there is any doubt, and all full-text papers will then be reviewed by four reviewers (HB, AB, HS, PD, KD) before a final decision is made following the strict inclusion/exclusion criteria. Any disagreement or divergent opinions among the reviewers regarding the suitability of studies will be settled through discussion or the final decision of aninternal reviewer team (HB, AB,HS,PD, KD). To determine the degree of agreement among the reviewers' Cohen's Kappa value will be calculated[17].

A PRISMA flow diagram will be drawn to depict the study selection processes. Details of articles excluded at the second stage will be recorded along with the reason for exclusion.[18]



Data Extraction (Indicators & Process)

In a standardized, pre-piloted Excel data extraction form, publication details, study characteristics, and findings from the included studies that are pertinent to the research question will be recorded. The extracted information will include details about the followings:

Authors, Publication year, Country, Currency unit, Costing amount, Study design, Target population, Sample size, Overview and aim of the tests used, Comparator, Measures of cost-effectiveness, Model specification, Methods for collecting the sample for test, Total/average intervention costs, Incremental Cost Effectiveness Ratio (ICER), Sensitivity analysis, Specificity analysis, and funding source. The main reviewer will extract the data. The validity of the data extraction process will be independently checked for completeness and accuracy by a team of internal reviewers. Any discrepancies between the reviewers over the data extraction process will be identified and resolved by discussion amongst the team.

Quality Assessment of Included Studies

The systematic reviews will undergo a quality assessment using the PRISMA checklist[16] and RCTs using CONSORT[19]. The PRISMA checklist contains 27 items, and the CONSORT checklist contains 25 items which will be assessed to know the quality of the systematic review included in thisstudy.The papers will be scored according to three categories: poor quality (40-65%), goodquality (66-80%) and

excellent quality (81%or higher) as per PRISMA guidelines. An internal reviewer team willexamine the process for accuracy andcompleteness to validate the quality assessment process.

Risk of bias

We will use the Cochrane Risk of Bias tool to examine bias across five domains for randomized controlled trials[20]. For other designs, we will use the ROBINS-I tool [2021]. Three reviewers will use the appropriate tool to rate each included study independently. If queries or discrepancies regarding data extraction occur, these will be resolved by discussion between reviewers. If not resolved, the rest of theauthors will complete the risk of bias tool. Our statistician will review the paper and decide if no consensus is achieved.

Strategy for data synthesis

The systematic review results will be reported by describing study characteristics, participant characteristics and outcome results. For all outcomes considered, we will present summary data for each group and effect estimates and confidence intervals as feasible. A narrative synthesis will be formulated from the studies based on two types of outcomes- Clinical and Economical. The outcomes of the intervention of interest with data definition and indicators are placed in the table below.

Outcome	**Data Definition**	**Data Indicator**
Clinical (Tests Accuracy)	The accuracy of a test/method is its ability to differentiate the patient and healthy cases correctly[22].	Sensitivity and specificity
Economical	The direct, indirect, and intangible costs compared to the consequences of alternative medical tests/methods.	Incremental Cost-effectiveness Ratio

We will also describe our literature search results and the methodological quality and risk of bias results using tables, figures and text. The strength of the evidence will be determined using GRADE as appropriate[23]. We will evaluate whether we have sufficient data to conduct random effects meta-analysis. The clinical insight will be used for clinical heterogeneity, methodologists will assess for methodologicalheterogeneity and statistical heterogeneity will be calculated. As described below, we will explain potential heterogeneity via subgroup and meta-regression analyses.

Analysis of subgroups or subsets

We will explore the impact of covariates by conducting subgroup analyses across different age groups, ethnicities, settings (Public or private hospitals) and different types of screening and diagnostic methods in and by including covariates in the random effects model.

Cost-effectiveness

We will use the CHEERS statement to examine the reporting quality of the identified economic evaluations [24]. We will pool effects across studies using random effects meta-analysis models as

appropriate for specific outcomes and the data available for analysis. Key considerations for pooled analysis will be the number of studies identified, their quality and the consistency of cost and outcomes.

Ethics, amendments and dissemination

We will use only secondary de-identified data to address the research question; therefore, ethics approval is unwarranted. Any protocol amendments will be tracked against our PROSPERO record and outlined in the final publication. The review findings will be disseminated through presentations at appropriate forums and conferences. The completed review will be submitted for publication in peer-reviewed journals.

Discussion

The described protocol represents a regressive approach to undertaking a systematic review. A well-designed research methodology is going to generate large amounts of evidence-based data. Given the time required for systematic reviews, the suggested method will minimize research waste. Additionally, the results will synthesize earlier research to produce original, data-driven hypotheses for further studies that aim to analyze cervical cancer screening and diagnostic methodologies. This finding will serve as a basis for developing studies that can provide the answers to important research questions about cervical cancer screening.

Further, it is important to have evidence of the cost-effectiveness of the screening and diagnostic methods and tests for cervical cancer, as it has a very high prevalence and can be managed if detected early. It is important to reduce mortality and YLL. Finding cost-effective screening and diagnostic methods for cervical cancer will also help policymakers to implement the methods through government initiatives for early detection and management of cervical cancer without financial hardship.

The methods and results of our systematic review will be reported following the PRISMA statement. While this review will be completed with the utmost care, there might be some limitations. It is documented that a large range of cervical cancer screening measures reported in research prevents individual patient data analysis. Further, data must be included in data collation, comparison across studies and pooled analyses. So, for the missing data in the studies for this systematic review, the main investigator will be contacted, and the missing data will be requested from them to reduce the chances of any bias.

As outcomes, we assess sensitivity and specificity as measures of the diagnostic tests and incremental cost-effectiveness ratios. However, this systematic review will not explore calculating the negative and positive predictive values of the screening and diagnostic tests for cervical cancer. The details collected as part of the quality assessment and risk of bias will allow us to select high-quality studies atlow risk of bias. The planned sensitivity analyses on these features may help to identify factors that influence the performance of the test and the modulation of the identified diagnostic cut-offs. If sufficient high-quality studies are identified, the planned meta-analyses will provide evidence for India's most cost-effective screening and diagnostic methods to detect and diagnose cervical cancer.

Author Contributions

All authors made necessary modifications to the pertinent intellectual material. The finished manuscript has been read and approved by all authors. Each author acknowledged their responsibility for the entirety of the work.

Conflict of Interest

The authors declare no conflict of interest.

Transparency Statement

Lead author Diksha LNU affirms that this protocol for a systematic review is an honest, accurate, and transparent account of the study being reported; that no significant components of the investigation have been omitted; and that any differences from the study as intended (and registered) have been clarified.

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