REVIEW

The Short-Term Impact Of COVID-19 Pandemic on Cervical Cancer Screening: A Systematic Review and Meta-Analysis

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Abstract

Objective: A systematic review and meta-analysis were carried out to assess the pooled proportion of women screened for cervical cancer before and during the COVID-19 pandemic. **Methods:** After ruling out registered or ongoing systematic reviews in the PROSPERO database regarding the impact of the COVID-19 pandemic in cervical cancer screening, the protocol of our systematic review and meta-analysis was registered in PROSPERO (CRD42021279305). The electronic databases were searched for articles published in English between January 2020 and October 2021and the study was designed based on PRISMA guidelines updated in 2020. Meta-analysis was accomplished in STATA version 13.0 (College Station, Texas 77,845 USA). The pooled proportion of women who had undergone cervical cancer screening was reported with 95% CI. In order to quantify the heterogeneity, Chi^2 statistic (Q statistic) and I^2 index were used. **Results:** The meta-analysis included seven studies from Slovenia, Italy, Ontario (Canada), Scotland, Belgium, and the USA, comprising 403,986 women and 199,165 women who were screened for cervical cancer before the COVID-19 pandemic in 2019 and during the pandemic in 2020, respectively. The pooled proportion of women screened for cervical cancer in 2019 was 9.79% (95% CI 6.00%-13.59%, 95% prediction interval 0.42%-23.81%). During the pandemic, the pooled proportion of screened women declined to 4.24% (95% CI 2.77%-5.71%, 95% prediction interval 0.9%-17.49%). **Conclusion:** There was a substantial drop in the cervical cancer screening rate due to lockdowns and travel restrictions to curb the COVID-19 pandemic. Scaling up cervical cancer screening strategies is essential to prevent the long-term impact of cervical cancer burden.

Keywords: Cancer screening- COVID-19- SARS-CoV-2 infection

Introduction

COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has grimly affected the access to cancer screening and health care of cancer patients. Morbidity and mortality associated with the pandemic are increasing with the emergence of the SARS-CoV-2 variants over time. A recent study from Portugal reported up to 40% fall in the detection of new cancer cases with 70% decline in the incidence of cervical and prostate cancers each (Morais et al., 2021). The pandemic has adversely affected the timely detection and initiation of cancer treatment globally, increasing the overall mortality. Cervical cancer is the fourth most common female cancer, and almost 85% of these cancer patients reside in low-income countries (Bray et al., 2018). As per GLOBOCAN data, in the year 2020, worldwide, 342,000 women died of cervical cancer, which is considered a preventable and treatable cancer (Sung et al., 2021).

The lifetime increase in cervical cancer-related deaths with delayed treatment of 9 weeks was estimated to be 2.52%, which was increased to 3.8% if further deferred for six months (Gupta et al., 2021). As per COVID-19 and Cancer Global Modelling Consortium (CCGMC), the COVID-related disruptions in cervical cancer screening will result in 5%-6% additional cancer burden among women below the age of 50 years (Smith et al., 2021). Cervical cancer screening was more adversely affected in the low and middle-income countries compared to developed countries. Globally, non-essential health services such as cancer screening and treatment of cervical lesions were temporarily suspended, prioritizing the care of symptomatic COVID-19 cases. If pre-neoplastic lesions are not detected early and managed appropriately, progression to invasive cancers is the main concern.

Worldwide, the COVID-19 pandemic has resulted in the interruption of cervical cancer screening, delayed diagnoses, and inadequate treatment. Transportation of the health care workers and the target population to the cancer screening centres were affected by the stringent measures to contain the infection such as lockdowns, travel restrictions, quarantine and social distancing. Delayed detection of cancers owing to missed screening

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results in increased morbidity and mortality. Women from developing countries and marginalized communities are the worst affected due to the current scenario. Quantification of the impact of the COVID-19 pandemic on cervical cancer screening is vital for planning proactive strategies to address the inequities in screening aggravated by the current pandemic.

The aim of this systematic review and meta-analysis was to evaluate the short-term impact of the COVID-19 pandemic on cervical cancer screening coverage based on the number of eligible women screened before and during the pandemic. The population (study participants) included women attending cervical cancer screening before and during the COVID-19 pandemic. The outcome of interest was the proportion of women screened for cervical cancer before and during the pandemic with 95% confidence interval. The research question framed for reviewing the articles was what proportion of women amongst the target population were screened for cervical cancer before and during the COVID-19 pandemic.

Materials and Methods

The systematic review was initiated after ruling out registered or ongoing systematic reviews concerning this topic in the PROSPERO database. The study protocol was registered in PROSPERO: International prospective register of systematic reviews database (http: // www. crd. york.ac.uk/prospero/) with registration number (CRD42021279305). The electronic databases were searched for articles published in English between January 2020 and September 2021 based on standard systematic review guidelines by Cochrane collaboration (https:// www.cochrane.org) and Campbell Collaboration (htps:// www.campbellcollaboration.org). The study protocol was designed based on Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines updated in May 2020 (Page et al., 2021). The meta-analysis component was modified appropriately to synthesize the pooled proportion of women attending cervical cancer screening before and during the pandemic.

Description of the condition

SARS-Co-V-2: SARS-Co-V-2, initially termed as 2019 novel Coronavirus (2019-nCoV) was first identified in Wuhan city, China. The acute respiratory illness was declared an outbreak of international concern on Jan 30th, 2020, and later pandemic on Mar 11th, 2020, by WHO.

COVID-19: COVID-19 is a respiratory viral disease caused by the SARS-Co-V-2 virus.

Study protocol

An electronic search of PubMed/Medline, Scopus, and Google Scholar was carried out for all the articles published between January 2020 and October 2021 concerning the impact of the COVID-19 pandemic on cervical cancer screening. The relevant articles in English involving human subjects were identified using search terms such as "impact" AND "COVID-19" OR "SARS-CoV-2" AND "cervical cancer screening."

Inclusion process and criteria

Studies reporting the number of women in the age group of 21-65 years screened for cervical cancer by cytology, Human Papillomavirus (HPV) DNA testing, or co-testing before and during the pandemic were included. Duplicate studies, irrelevant articles, brief reports, and articles published in languages other than English were excluded.

Data extraction

A validated proforma including the first author, year of publication, region, study design, the total number of the target population, number of participants screened in 2019 and 2020, screening method, and test volume reduction in percentage was prepared. A three-stage selection process was carried out for the final inclusion of the studies. One reviewer assessed titles from 958 records for relevance for inclusion in the study. Studies applicable to the review were moved to the second stage after excluding irrelevant topics and duplicates (n=107). In the second stage, two reviewers independently obtained the abstracts of the studies (n=32) and analyzed them. After reviewing the abstracts, full texts of studies (n=15) were retrieved, and two reviewers examined independently. Corresponding authors were contacted electronically if further clarifications were needed or studies reported only the reduction in the test volume or test rate per 100-person months. The references of retrieved articles were also reviewed to increase the search sensitivity. The study selection process was depicted in the PRISMA chart (Figure 1). The last date of the search was Oct 30th, 2021.

Quality assessment (Risk of bias in individual studies)

We used the National Institutes of Health checklist for observational, cohort, and cross-sectional studies to assess the risk of bias in individual studies (quality assessment), chosen after the abstract and content review ("Study Quality Assessment Tools | NHLBI, NIH" n.d.). The studies with a minimum score of eight or above, seven, or five or less than five "Yes responses" were considered good, fair, and poor quality, respectively. For cross-sectional and case-control studies, question numbers 1, 2, 3, 4, 5, and 11 were applicable. The responses to the remaining eight questions (6-10,12,13,14) were marked as not applicable (NA). Each question was categorised as Yes, No, others-CD (can-not determine), NA (not applicable), NR (not reported). The studies with six "Yes" responses were considered good, and those with four /five were taken as fair. The studies with less than four "Yes responses" were considered of poor quality. Two reviewers assessed the quality of the studies.

Statistical analysis

Meta-analysis was accomplished in STATA version 13.0 (College Station, Texas 77,845 USA). The forest plots were constructed using metaprop package in STATA. A considerable amount of heterogeneity across the studies was anticipated as the included studies were mostly observational. The pooled proportion of women undergoing cervical cancer screening was reported with 95% CI along with Chi^2 statistic (Q statistic) and

I^2 index to quantify the heterogeneity. The I^2 value ranging between 0% to 24% indicates consistency. The I^2 values of 25%-49% and 50-74% point toward low and moderate heterogeneity, respectively. In studies with high heterogeneity, the I^2 value varied between 75%-100%.

Assessment of Publication bias

Egger's test was employed to analyse the publication bias (Egger et al., 1997). Weighted linear regression with standardised effect estimate and precision are the dependent variable and independent variable, respectively. In the present study, loge proportion of women undergoing screening was considered the effect estimate, and the precision will be taken as 1/standard error of loge proportion rate. Weights were allotted using the inverse variance approach (1/variance of the effect estimate). A statistically significant bias coefficient provides evidence for publication bias.

Results

Included studies

There are seven studies from Slovenia, Italy, Ontario (Canada), Scotland, Belgium, and the US, including 403,986 screened women before the pandemic in 2019 and 199,165 screened women during the pandemic in 2020 (Miller et al., 2021; Ivanuš et al., 2021; Martellucci et al., 2021; Meggetto et al., 2021; Masson et al., 2021; de Pelsemaeker et al., 2021; DeGroff et al., 2021). All these studies were qualified as good. One qualified study was based on the data from The National Breast and Cervical Cancer Early Detection Program (NBCCEDP) by the Centers for Disease Control and Prevention (CDC), which offers breast and cervical cancer detection testing to socially deprived, under-resourced and marginalized women from selective regions in the US(De Groff et al., 2021). This study reported the lowest screening coverage before as well as during the pandemic. Meanwhile, a Slovenian study based on the population-based cervical cancer screening known as Zora registry reported the highest screening deficit of 92% during the pandemic (Ivanuš et al., 2021). Data regarding the high-grade cytological abnormalities/cervical intraepithelial neoplasia (CIN2+) among the screened population was reported in only two studies (Ivanuš et al., 2021; Meggetto et al., 2021). Amongst the target population, the percentage of screened women ranged from 0.36% to 28.8% in 2019 (Table 1). Meanwhile, during the pandemic, the screening coverage declined from 10.2% to 0.04%, and the overall screening deficit varied between 43.3% and 92%.
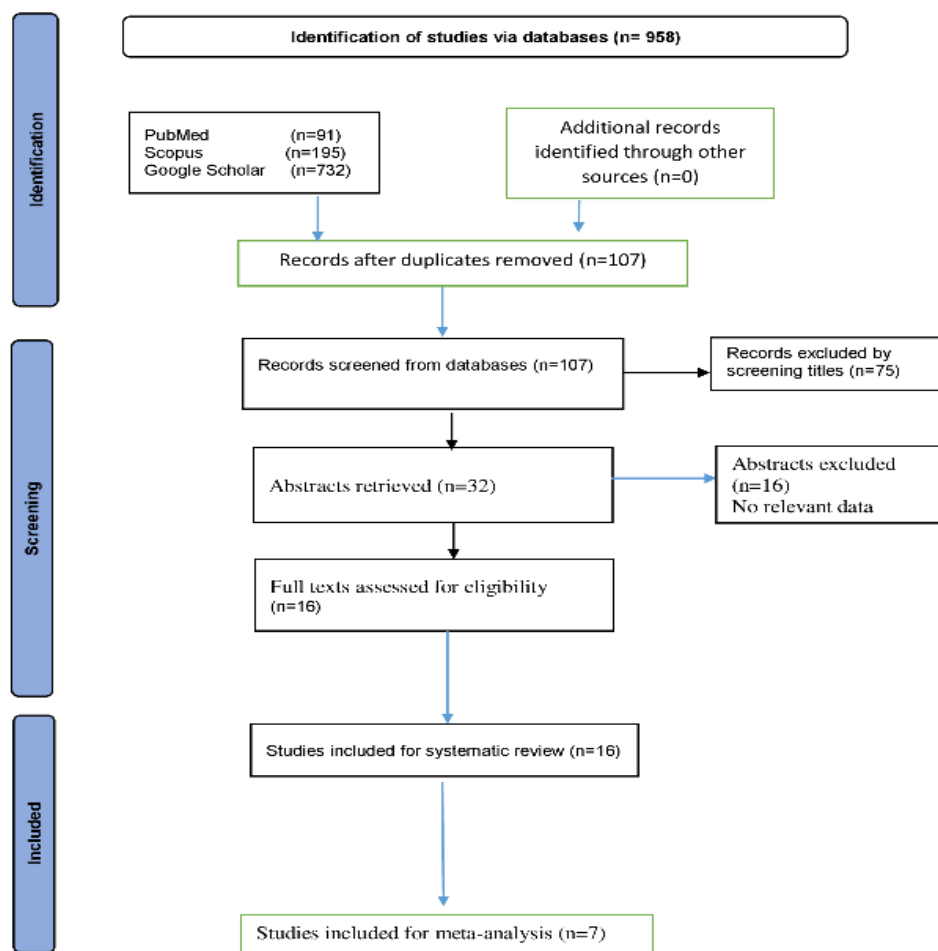

Figure 1. PRISMA 2020 Flow Diagram for Updated Systematic Reviews which Included Searches for Databases, Registers and Records Identified through Other Sources (Page et al., 2021). The flow diagram illustrates the number of studies identified, screened, abstracts/full-text articles excluded and retrieved for the systematic review and meta-analysis

Table 1. Main Characteristics of the Studies Included for the Meta-Analysis

| S No	Study (year)	Region	Study design	Age in years	Target population (N) 2019	Age in years	Women Screened in 2019 (N)	Percentage Screened 2019 (%)	Target population in 2020 (N)	Women Screened in 2020 (number) (N)	Percentage Screened 2020 (%)	Period (Months)	Screening modality	Test volume reduction (%)	Quality of studies
1	Miller et al 2021 Jan	California	retrospective observational	21-65	1,455,244	21-65	229,019	15.7	1,492,442	152490	10.2	9	Cytology /co-testing	21-29yrs 78.0 30-65yrs 84.0	Good
2	Urska Ivanus Apr-21	Slovenia	retrospective observational	20-64	593,695	20-64	29,441	4.9	593,695	3,131	0.52	2	Cytology	92	Good
3	Martelluci May-21	Italy	retrospective observational	21-65	43,100	21-65	12,415	28.8	43,100	4411	10.2	6	Cytology	64.5	Good
4	Meggetto et al May-21	Ontario Canada	retrospective observational	21-69	1,000,000	21-69	81,877	8.1	1,000,000	21,947	2.2	6	Cytology	85.8-41.0	Good
5	Masson May-21	Scotland	retrospective observational	25-65	1,010,963	25-65	25,927	2.5	1,010,963	11,209	1.1	4	Cytology/HPV test	57	Good
6	De Pelsemaeker Jun-21	Belgium	retrospective observational	25-65	74,593	25-65	5941	7.9	62,727	3370	5.3	6	Cytology	43.3	Good
7	DeGroff Jun-21	USA	retrospective observational	21-65	5,300,000	21-65	19,366	0.36	5,300,000	2607	0.04	6	Pap test/ HPV test/co-testing	84	Good
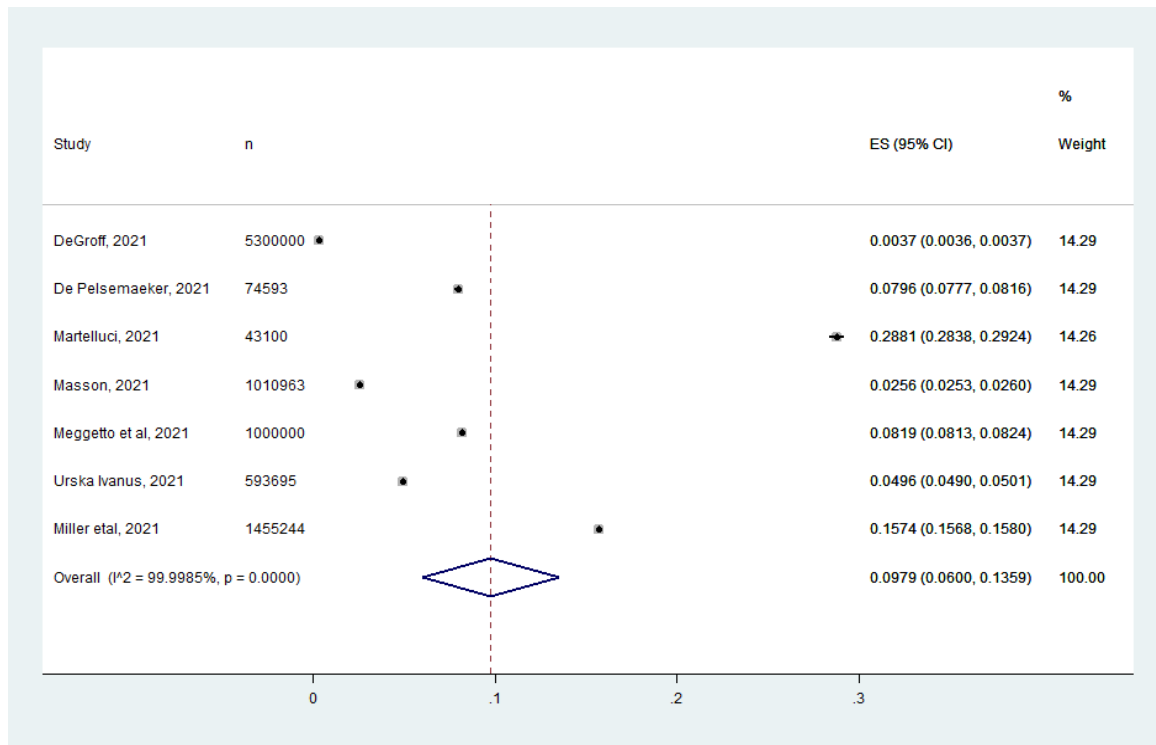
Figure 2. The Forest Plot of the Proportion of Women Screened before the COVID-19 Pandemic Using Random Effects Model amongst the Target Population. Squares indicate the effect size of individual studies and the extended lines denote 95% confidence intervals (CI). Sizes of squares imply the weight of studies based on sample size using a random effects analysis. The diamond data indicates pooled prevalence. Test of heterogeneity: I^2=99.62%, p-value=0.00.

Meta-analysis

The pooled proportion of women screened in 2019 was 9.79% (95% CI 6.00%-13.59%, 95% prediction interval 0.42%-23.81%).). The pooled proportion of women who had undergone screening was 4.24% (95% CI 2.77-5.7%, 95% prediction interval 0.9%-17.49%) during the current COVID-19 pandemic in 2020. As the I^2-value was>90%, a high heterogeneity was observed between the studies.
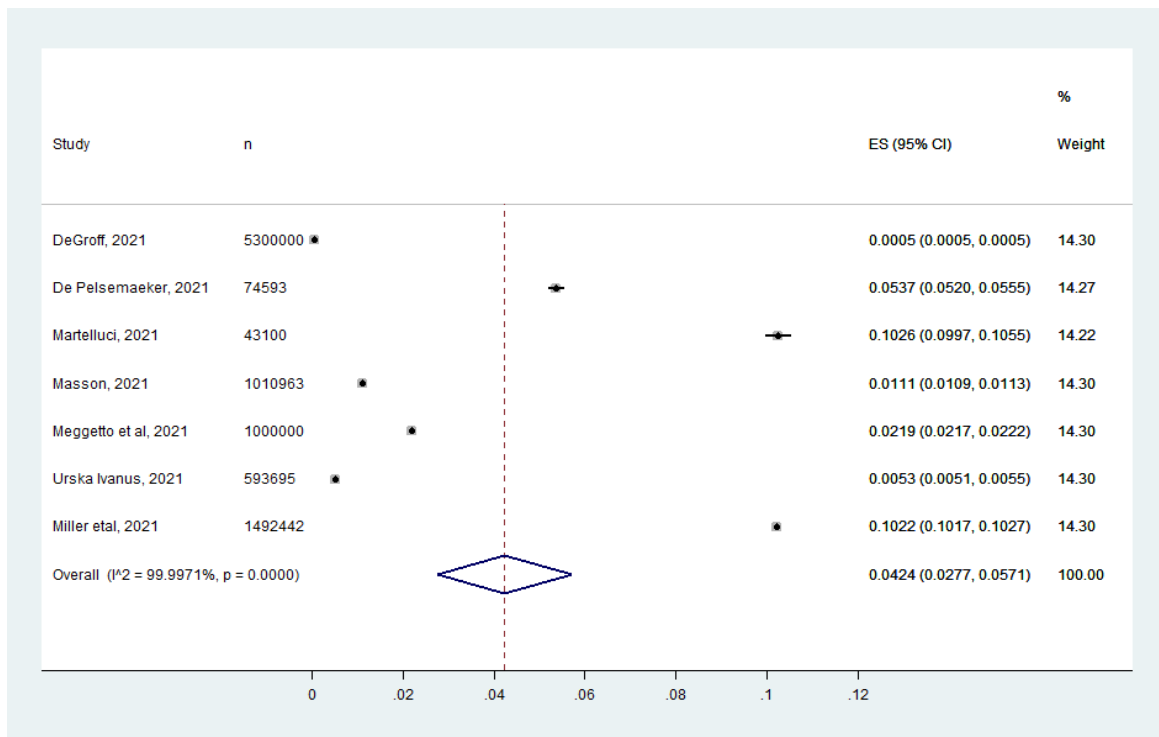

Figure 3. The Forest Plot of the Proportion of Women Screened during the COVID-19 Pandemic Using Random Effects Model. Squares indicate the effect size of individual studies and the extended lines denote 95% confidence intervals (CI). Sizes of squares imply the weight of studies based on sample size using a random effects analysis. The diamond data indicates pooled prevalence. Test of heterogeneity: I^2= 99.99 %, p=0.00.

Table 2. Table Depicts the Results of Egger's Test for Publication Bias

Coefficient	Estimate with 95% CI	P-value
Publications related to impact of COVID-19 on cervical cancer screening		
Slope	-0.0009 (-0.0047, 0.0028)	0.552
Bias	147.8932 (-4.4266, 300.213)	0.055

CI, confidence interval

Publication bias

There was no publication bias as the p-value for the bias coefficient was not statistically significant (Table 2).

Discussion

Globally, the COVID-19 pandemic has profoundly interrupted cervical cancer screening programs. All the qualified studies included for the quantitative analysis were from developed countries having organized cancer screening programs. The reduced screening coverage will be translated as a higher incidence of invasive cancers in the coming decades. A significant decrease in cervical cancer screening rate was observed among ethnic minority groups and women with inadequate healthcare in the US (DeGroff et al., 2021). Slovenian study reported the highest screening deficit of cytology smears among women in the age group of 30-39 years. This age group constituted a group of vulnerable women with an increased frequency of high-grade cytological abnormalities ($\geq$CIN2+) (Ivanuš et al., 2021). Miller et al. also reported higher test volume reduction among women above 30 years during the pandemic (Miller et al., 2021). The data from the Pathology laboratory in Belgium observed a considerable reduction in the number of cervical cytology smears and breast biopsies for gynecological cancer screening during the initial months of the pandemic (de Pelsemaeker et al., 2021). Meanwhile, the number of histopathological samples from central nervous system lesions was comparatively stable during the pandemic, and surgical care for malignant patients was unaffected. In Australia, A decline in cervical cancer screening rate was expected due to the modification of screening interval in 2020 from three yearly Pap smears to five-yearly HPV testing ("Cancer Screening and COVID-19 in Australia, How Has COVID-19 Affected Australia's Cancer Screening Programs? - Australian Institute of Health and Welfare" n.d.; Feletto et al., 2020). Australian data did not include the information from the first year of implementation, ("Cancer Screening Programs: Quarterly Data, National Cervical Screening Program" n.d.). Four qualified studies compared the number of women screened six months prior and six months during the pandemic (Martellucci et al., 2021; Meggetto et al., 2021; de Pelsemaeker et al., 2021; DeGroff et al., 2021). Miller et al. compared the number of women screened in the initial nine months before the pandemic in 2019 with corresponding months in 2020 (Miller et al., 2021). Meanwhile, the study from Scotland included the number of women screened during the five months before the complete suspension of the screening programme and the number of women screened in four months after the resumption of screening. This meta-analysis emphasizes the importance of maintaining cancer screening during challenging times. We could include data from socially deprived and ethnic minority populations from the United States despite the non-availability of published studies from developing countries.

There was heterogeneity in the number of months during which women were screened, screening assays employed, and screening intervals in qualified studies. The screening methods employed were cytology, HPV test, or co-testing in studies from California, Scotland, and certain regions in the US, as shown in the Table 1. The remaining studies reported the number of women screened by cytology alone at an interval of three years before and during the pandemic. Lengthening of screening intervals happened when the target population was subjected to only HPV testing. Since March 2020, Scotland has introduced HPV DNA testing as the primary cervical cancer screening test replacing cytology. Women in the age group of 50-65 years were screened every five years irrespective of the screening method.

The main limitation of our meta-analysis was that the data from developing countries concerning cervical cancer screening coverage during the COVID-19 pandemic could not be incorporated due to a lack of published reports. We could not assess the pooled proportion of women having high-grade cervical abnormalities during the pandemic as only two studies provided the data. Cervical cancer screening was comparatively less disrupted in the UK during the pandemic (Wilson et al., 2021). In the same way, the cervical cancer screening deficit was effectively managed with the help of obstetricians and gynecologists in Ancona Province of Italy (Martellucci et al., 2021). As per the Zora registry, the cervical cancer screening deficit during the first wave of the pandemic was effectively managed by rigorous scaling-up measures in the second wave. However, the pandemic-associated disruption in cervical cancer screening is much more in low-and middle-income countries. Cancer screening and treatment facilities were partially or completely transformed to COVID hospitals in developing countries (Bashar and Begam, 2021). The social and healthcare-associated inequities are further intensified during the current pandemic (Wentzensen et al., 2021). These underserved persons already encounter cancer screening and management disparities due to low income, ethnicity, rurality, migrant status and gender. The personal and structural barriers to cancer screening can be overcome by self-collection of vaginal samples during stay-at-home orders or advisories denying access to the screening centres (Ajenifuja et al., 2020) similar to the use of stool-based tests at home for colon cancer screening. Self-sampling is a promising strategy even though not approved for cervical cancer screening globally, and self-collection of vaginal samples may facilitate better screening coverage. Implementation of risk stratification methods is another option during challenging times to screen women who are at higher risk.

Public health measures to deal with the huge cancer screening deficits should be undertaken. During the current COVID-19 pandemic cancer screening and timely management have to be maintained while protecting the

patients and care givers (Dewi, L., 2020). If policymakers prioritize the screening of high-risk women as well as extending the screening intervals of low-risk women, long-term consequences can be avoided. In addition women who missed the screening due to the COVID-19 related restrictions have to be given precedence over others (Castanon et al., 2020). Data from transitioning countries concerning the number of women being screened and having high-grade cervical abnormalities during the COVID-19 pandemic are essential. The current pandemic provides an opportunity for self-collection of vaginal samples, possibly furthering the screening coverage rate.

Author Contribution Statement

The authors confirm contribution to the paper as follows: Study conception and design: S Sabeena Data Collection: S Sabeena, N Ravishankar, Analysis and interpretation of results: S Sabeena, N Ravishankar Draft manuscript preparation: S Sabeena, All authors reviewed the results and approved the final version of the manuscript.

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