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HIV infection and pre-cancerous cervical lesions in Ethiopia: A systematic review and meta-analysis

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ABSTRACT

Background

Cervical cancer is potentially preventable and an important health issue for women around the world. In 2010, it was estimated that 20.9 million women were at risk of developing cervical cancer in Ethiopia with an estimated 4,648 and 3,235 annual numbers of new cases and deaths, respectively. In this paper, we aim to determine the impact of HIV status on pre-cancerous cervical lesions (PCCL).

Methods

Using a systematic review and meta-analysis, we searched the literature for studies evaluating the relationship between HIV status and pre-cancerous cervical lesions. Data were summarized using fixed effect models.

Results

Nine out of 360 records identified through database searching met our inclusion criteria. The pooled odds ratios for pre-cancerous cervical lesions, comparing women who are HIV positive versus women who are HIV negative, was OR 1.75 (95% CI: 1.40, 2.18), $P < 0.00001$, $I^2 = 0\%$).

Conclusions

These findings support the hypothesis that HIV positive status has a marked effect on PCCL and the risk of PCCL. Government and other stakeholders should give patients living with HIV high priority for cervical cancer screening.

Keywords: Cervical cancer, Ethiopia, HIV, Meta-analysis, Pre-cancerous lesions, Systematic review

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INTRODUCTION

It is estimated that more than a million women worldwide are currently living with cervical cancer (CC).[1] Global cancer statistics indicate that CC ranked fourth for both incidence (6.6%) and mortality (3.5%) among women in 2018.[2] About 85% of new cases and 87% of all deaths of CC occur in less developed regions.[3] In Ethiopia, cervical cancer is the second largest cause of cancer deaths among women aged 15–44 years (breast cancer is the highest).[4] The joint United Nations programme on HIV/AIDS (UNAIDS) estimates that 36.9 million [CI 31.1 million–43.9 million] people were HIV positive in 2017 and around 7,000 young women aged 15–24 become infected with HIV every week.[5] The reported HIV/AIDS prevalence among women aged 15–49 years in the 2016 Ethiopian Demographic and Health Survey was 1.2%.[6]

According to the World Health Organization, in areas where HIV is endemic cervical cancer screening results may be positive for pre-cancerous lesions in 15-20% of the target population.[1] In women with HIV, a cervical pre-cancer might develop into an invasive

cancer faster than in women who are HIV negative.[7] Around 534,000 women over the age of 15 living with HIV in Ethiopia are vulnerable to cervical cancer, since women infected with HIV/AIDS are at ten times higher risk for pre-cancerous lesions.[8] Few studies have been conducted in Ethiopia to assess the predictors of pre-cancerous cervical lesions (PCCL), however. Factors identified by the existing studies include: older age, having multiple sexual partners, age at first sexual intercourse (years) and history of STI.[9-12] The precursor stage of cervical cancer can last for many years before becoming invasive. When the cancer advances, the following symptoms may be observed during sex: abnormal vaginal bleeding, pelvic pain, vaginal discharge and pain.[13]

Common screening methods include conventional (Pap) and liquid based cytology (LBC), HPV (Human papillomavirus) testing for high-risk HPV types (e.g. 16 and 18) and Visual Inspection with Acetic Acid (VIA). VIA followed by treatment is an effective, relatively simple procedure that is feasible in resource-limited areas.[14]

The Sustainable Development Goals aim to reduce premature mortality from non-communicable diseases (NCDs) by one third by 2030; this includes cervical cancer as it is the second most common cause of cancer-associated mortality for women globally.[15]

Despite having a national cancer control plan to reduce cancer incidence and mortality in Ethiopia by 15% by 2020, cancer research in Ethiopia is not commensurate with the magnitude of the problem.[16] Studies show inconsistent and inconclusive association between HIV and pre-cancerous cervical lesions (PCCL). Therefore, this systematic review and meta-analysis was designed to link the twin burdens of HIV and PCCL by establishing an association between HIV and PCCL in Ethiopia.

METHODS AND MATERIALS

We undertook a systematic review that included a meta-analysis; as existing review protocol was not available, we did not register in Cochran's library. We followed the PRISMA statement for reporting systematic reviews recommended by the Cochrane Collaboration.[17] Observational studies (case control and cross-sectional studies) on HIV status and PCCL were included in our meta-analysis. Following PRISMA guidelines, two investigators retrieved studies through an internet search from the electronic databases of PubMed, Google Scholar, Web of Science and Scopus. The search was undertaken between November 2 and 4, 2020.

Searches were performed using selected search terms under two search themes that were combined using the Boolean operator 'and'. For the first theme, 'Pre-cancerous cervical lesion', a combination of text words were used: 'cervical cancer', 'cervical cancer and HIV status', 'pre-cancerous cervical lesion', 'Visual inspection with acetic acid', 'cervical cancer screening', 'factor of cervical cancer', 'pre-cancerous cervical lesion+HIV status Ethiopia'. For the second theme, of 'HIV status', the terms 'positive' and 'other population group' was used.

Inclusion criteria

Studies were included in the review if: (1) the study was an observational study (cross-sectional study, case-control study, or cohort study), (2) the outcome of interest was PCCL, (3) the study reported the number of pre-cancerous cervical lesions, according to HIV status, (4) the study recorded a score of 5 or above on the Newcastle-Ottawa Scale (NOS) – an ongoing collaboration between the University of Ottawa, Canada and the University of Newcastle, Australia to develop a score that can be used to assess the quality of nonrandomized studies in meta-anaylses, which rates studies from 1 to 10 – or on an adapted Newcastle-Ottawa Scale (NOS), and (5) the studies were published between 2015 and 2020.

Exclusion criteria

Studies that did not include participants with pre-cancerous cervical lesions according to HIV status, and studies that had not been conducted in Ethiopia were excluded to avoid a combination of studies that were not comparable.

A flow diagram showing the search criteria, eligibility screening and selected papers is shown in fig 1. This process returned nine studies for inclusion.

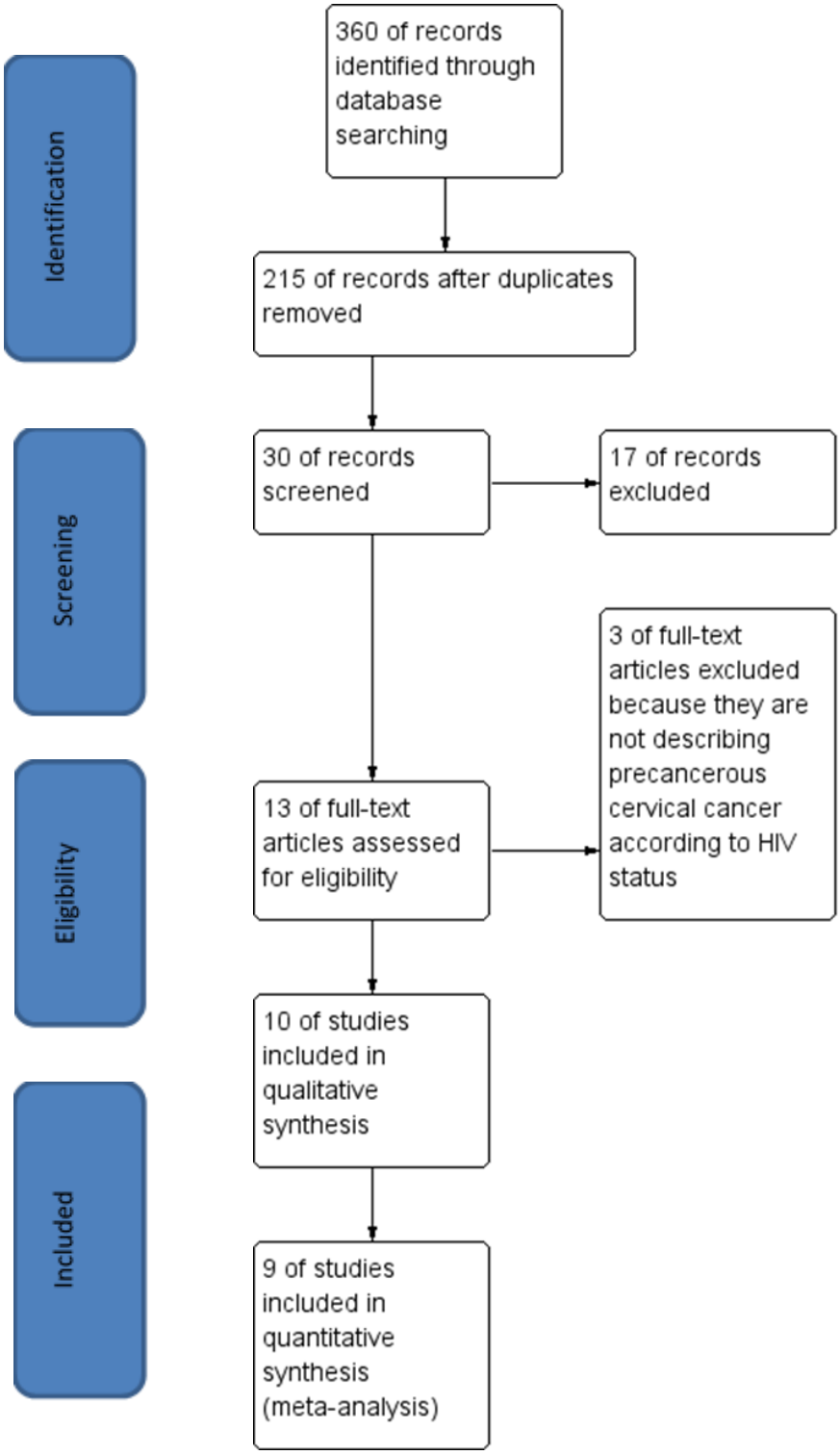

Fig 1 PRISMA Flow Diagram of Studies' Screening and Selection

Data extraction and quality assessment

The data extraction and quality assessment was performed by three reviewers, who were not involved in the internet search, from electronic databases to reduce bias. The following information was extracted from each eligible study: first author's name, study design, source of study population, sample size, number of HIV positive and HIV negative participants, and definition of PCCL. All studies were conducted by multi-variable analysis; variables that were fully adjusted for potential confounding were selected. Quality assessment was conducted using the 10-star Newcastle Ottawa Quality Assessment Scale (NOS).[18] We included studies with an NOS score greater than 5. Three authors assessed the articles for inclusion in the review (fig 1). Disagreements between assessors were managed through discussion and majority decisions among the three reviewers.

Outcome measurement

Assessment of PCCLs was conducted using the screening method Visual Inspection of the Cervix with Acetic Acid (VIA), which involves naked-eye inspection of the uterine cervix one minute after application of a 3–5% solution of acetic acid using a cotton swab or a spray.[8, 19]

Women were diagnosed as having PCCL if they returned a VIA result of raised and thickened white plaques or acetowhite epithelium, usually near the squamo-columnar junction (SCJ). They were considered not to be showing evidence of PCCL if the VIA indicated a smooth, pink, uniform and featureless cervix. Evidence of cervical ectropion; polyp; cervicitis; inflammation; and/or nabothian cyst after applying a dilute solution of acetic acid were noted, but not considered to be evidence of PCCL.[8,19]

Publication bias and heterogeneity

We quantified the existence of heterogeneity with I^2 and its corresponding p-value. A value of 25%, 50%, and 75% was used to declare the heterogeneity test as low, medium and high respectively.[20] Publication bias was checked subjectively through observing the funnel plot and objectively through Egger's regression test. Statistically significant publication bias was declared at a p-value > 0.05 at 95% CI.

Analysis of data

The meta-analysis was conducted using Revman software (version 5.3) and Meta essential software. The relationship between HIV status and PCCL was examined using the prevalence of PCCL in HIV positive versus HIV negative women. A meta-analysis compared PCCL between HIV positive and HIV negative women in all included studies.

A fixed-effects model was used to estimate the pooled ORs with 95% CIs as there was no evidence of heterogeneity.[21] Forest plots were used to present the pooled estimate with the 95% confidence interval (CI). All statistical tests were two sided and a p-value <0.05 was considered statistically significant.

RESULTS

Study searches and selection

The initial search returned 360 records from different electronic search databases including Pub Med, Google Scholar, Web of Science and Scopus. From this, 215 duplicate records were removed and 17 records were excluded after screening by title and abstracts.

We assessed the full texts of 13 remaining records for eligibility and three records were further excluded as they did not meet the inclusion and exclusion criteria. One additional text was excluded due to a methodological issue. After review, nine studies were included for systemic review and meta-analysis (9-12, 22-26) to estimate the pooled adjusted odds ratio of HIV status with pre-cancerous cervical lesion (fig 1).

Characteristics of the studies

The nine included studies were published between 2015 and 2020. All the studies included in the review were observational (case-control, cross-sectional studies). A total of 2,949 women were examined in the analyses. The included studies reported sample sizes ranging between 164 (study 10) and 528 (study 25); see table 1. Of 818 (27.7%) HIV positive study participants, 205 (25.1%) had evidence of PCCL. Among 2,131 (72.3%) HIV negative participants, 433 (20.3%) had evidence of PCCL. The overall prevalence of PCCL was 6.95% in HIV negative participants and 14.68% in HIV positive participants.

Table 1 Characteristics of studies for HIV infection and PCCL among women in Ethiopia, 2020 (n=9)

Articles	Sample size	Title/Study design	HIV Status	PCCL		Ref
				Yes	No	
Adella. G	407	Predictors of pre-cancerous cervical lesions among women screened for cervical cancer in Bahir Dar Town, Ethiopia: a case–control study	Positive	17	44	11
			Negative	83	247	
Assefa. A	391	Prevalence and predictors of Pap smear cervical epithelial cell abnormality among HIV-positive and negative women attending gynecological examination in cervical cancer screening center at Debre Markos referral hospital, East Gojjam, Northwest Ethiopia: a comparative cross-sectional study	Positive	35	162	12
			Negative	20	174	
Deksissa. Z	334	Prevalence and factors associated with VIA positive result among clients screened at Family Guidance Association of Ethiopia, south west area office, Jimma model clinic, Jimma, Ethiopia 2013: a cross-sectional study	Positive	21	113	22
			Negative	20	148	
Derbie. A	428	Cervical lesion detection using visual inspection with acetic acid and associated factors among Ethiopian women: A facility-based cross-sectional study	Positive	33	161	26
			Negative	14	107	
Gebremariam. A	343	Factors associated with cervical pre-cancerous lesions among women screened for cervical cancer in Addis Ababa, Ethiopia: A case control study	Positive	46	53	9
			Negative	67	173	
Kassa. R	164	Risk factors associated with pre-cancerous cervical lesion among women screened at Marie Stops Ethiopia, Adama Town, Ethiopia 2017: a case control study	Positive	9	9	10
			Negative	33	74	
Misgina. K	342	Prevalence of pre-cancerous cervical lesion and associated factors among women in North Ethiopia: an institution-based cross-sectional study	Positive	1	15	23
			Negative	22	304	
Teka. T	528	Magnitude and factors associated with pre-cervical cancer among screened women in Southern Ethiopia: a facility based cross-sectional study	Positive	17	21	25
			Negative	129	361	
Tekalegn. Y	222	Determinants of VIA positivity among women screened for cervical pre-cancerous lesion in public hospitals of Oromia Region, Ethiopia: unmatched case-control study	Positive	26	35	24
			Negative	45	110	

Association between HIV status and PCCL

The pooled adjusted odds ratios for pre-cancerous cervical lesion comparing Women who are HIV positive versus Women who are HIV negative was OR 1.75 (95% CI: 1.40, 2.18), P < 0.00001, I^2 = 0%). There was no significant heterogeneity among the 9 studies (Chi^2 = 4.66, DF = 8 I^2 = 0% and P = 0.793). (Fig.2). We assessed the funnel plot for asymmetry by visual inspection for pre-cancerous lesion and HIV status. No publication bias was observed (Egger's test, p=0.455 and Begg's test, p=0.532).

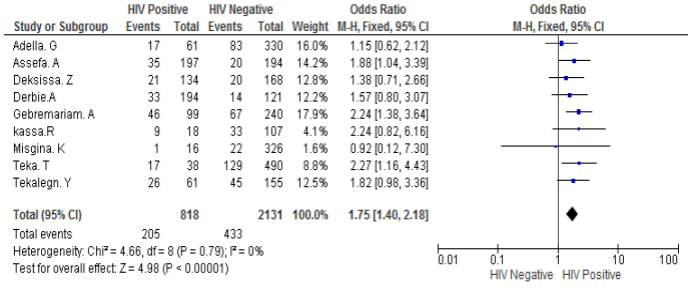

Fig 2: Forest plot for effect of HIV infection on PCCL on women in Ethiopia, 2020.

Table 2 NOS score of studies for HIV infection and PCCL among women in Ethiopia, 2020 (n=9)

Study	Selection	Comparability	Outcome	NOS scale
Adela.G	***	**	***	8
Assefa.A	***	**	**	7
Dekissesa.Z	***	**	*	6
Derbie. A	***	**	**	7
Geberemariam.A	***	**	***	8
Kassa. R	***	**	**	7
Misgna.K	***	**	***	8
Teka.T	***	**	*	6
Tekalegne.Y	***	**	*	6

**Each star represents a high-quality criterion accomplished by the study.*

DISCUSSION

This meta-analysis determined the association between HIV status and pre-cancerous cervical lesions among woman in Ethiopia using nine studies. This study revealed that 628 (21.6%) of the women were positive for pre-cancerous cervical lesions. According to the results of this meta-analysis, the pooled adjusted odds ratios for all studies revealed that odds of PCCL in Ethiopia among HIV positive women is 1.76 times higher than in HIV negative women (OR 1.75; 95% CI: 1.49, 2.18, $P < 10^{-6}$, I^2= 0%).This finding is consistent with several previous studies conducted in Tanzania,[27,28] Swaziland,[29] Zimbabwe,[30] South Africa,[31] Dessie[32] and Yirgalem[33] all of which show association between HIV and pre-cancerous cervical lesions. The findings of our study is also supported by other studies in Kenya[34] and Senegal[35] which report an increased risk of cervical dysplasia among HIV positive women compared with those who are HIV negative. This could be due to the effect of HIV on the immune system.[36] Additionally, HIV infection was associated with higher incidence and reduced clearance of HPV infection.[37] However, the results of this study differ from a previous study undertaken in Rwanda[38] and several studies conducted in different parts of Ethiopia[9-12, 22-26] where no association between HIV status and pre-cancerous cervical lesions among women could be determined. These discrepancies could be explained in part by differences in lifestyle factors such as sociocultural characteristics, nutritional, environmental, sexual behaviour and hygiene amongst the study populations. The varying associations may also reflect differences in the sample size of the studies.

This study has some limitations. First, cases and controls were identified only via their current VIA result; due to the validity of this screening test, cases and controls could be misclassified. This might contribute to underestimating the cause-and-effect relationship between some of the explanatory variables and the outcome of interest: PCCL. Second, despite the fact that Egger's test and Begg's funnel plots detected no evidence of publication bias in the meta-analysis, estimation may not be sufficiently accurate due to the small number of included studies.

CONCLUSIONS

Cervical cancer continues to be a public health challenge in Ethiopia. The findings of this systematic review suggest a positive association between HIV status and pre-cervical cervical lesions. This suggests that regular screening of HIV-infected women is of paramount importance. The success of any such strategy will be highly dependent on expanding access to all HIV-infected women and obtaining a high follow-up rate from the point of screening. Our results suggest that conducting well-designed prospective cohort studies to investigate the natural history of pre-cervical cervical lesions among HIV infected women in Ethiopia is warranted.

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