

## Hiv Infection and Pre-Cancerous Cervical Lesion Among Women in Ethiopia: A Systemic Review and Meta-Analysis

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### Abstract

**Background:** Cervical cancer is the second most prevalent cancer among women in the developing countries including Ethiopia. Precancerous lesions can be developed and risk to the development of cervical cancer over time. Early identification of the precancerous lesion and its risk factor is paramount in preventing cervical cancer.

**Objective:** The aim of this study was to determine the impact of HIV status on pre-cancerous cervical lesions.

**Methods:** Searches were carried out in Pub Med, Google Scholar, web of science and Scopus. Studies were selected for meta-analysis if they reported the number of pre-cancerous cervical lesion, according to HIV status. For critical appraisal of studies, Newcastle-Ottawa Quality Assessment Scale (NOS) was used. The analysis was conducted by using meta-essential and Revman software. To test the heterogeneity of studies, the Cochran Q test and I<sup>2</sup> test statistics were used. To detect publication bias of the studies, the funnel plot and Egger's test were used. The pooled prevalence of cervical cancer screening and the odds ratio (OR) with a 95% confidence interval was presented using forest plots.

**Results:** Overall, 9 of 360 records identified through database searching met inclusion criteria. 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<sup>2</sup>=0%.

**Conclusion:** These findings support the hypothesis that being HIV positive has a marked effect on PCC L and the risk of PCCL. Government and other stakeholders should give high priority in early screening of cervical cancer for patients living with HIV.s.

**Keywords:** Cervical cancer; Ethiopia; HIV; Meta-analysis; Precancerous lesions; Systematic review

### Introduction

Cervical Cancer (CC) is one of the gravest threats to women's lives. Precancerous lesions are biologically defined as lesions that can progress potentially to invasive cervical cancer if left untreated [1].

It is estimated that over a million women worldwide currently have cervical cancer [1]. Global cancer statistics indicate that CC ranks fourth for both incidence (6.6%) and mortality (3.5%) among females in 2018 [2]. About 85% of new cases and 87% of all deaths of CC occur in the less developed regions [3]. In Ethiopia, cervical cancer is the second most cause of cancer deaths among women aged 15 to 44 years next to breast cancer [4].

The joint united nations programme on HIV/AIDS (UNAIDS) estimates that 36.9 million [31.1 million-43.9 million] people were HIV positives in 2017 and around 7000 young women aged 15-24 years become infected with HIV Every week [5]. According to Ethiopian Demographic and Health Survey 2016 report HIV/AIDS prevalence among women aged 15 to 49 years was 1.2% [6].

According to a World Health Organization, in areas where HIV is endemic, cervical cancer screening results may be positive for precancerous 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 it normally would [7]. About 534,000 women over age 15 living with HIV in Ethiopia are among the most vulnerable to cervical cancer since women infected with HIV/AIDS are ten times at higher risk for precancerous lesions [8]. In Ethiopia, few studies have been conducted to assess the predictors of the cervical precancerous lesion. Factors identified by those studies were: being in the older age group, having multiple sexual partners, Age of first intercourse (years), history of STI [9-12].

Precursor stage of cervical cancer lasts many years before becoming invasive cancer but when it became advanced the following symptoms

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like; abnormal vaginal bleeding, pelvic pain, vaginal discharge and pain during sex will be observed [13].

Conventional (Pap) and Liquid Based Cytology (LBC), HPV (Human Papilloma Virus) testing for high risk HPV types (e.g. types 16 and 18) and Visual inspection with Acetic Acid (*via*) are commonly used methods for screening; but *via* followed by treatment is an effective method, relatively simple procedure and feasible in resource limited areas[14]. The 2030 Sustainable Development Goals on non-communicable diseases (NCD's) is to reduce by one third premature mortality from NCD's which extends to cervical cancer, the second most common cause of cancer associated mortality for women [15].

Despite having 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 infection and pre-cancerous cervical cancer (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.

## Materials and Methods

### Study design

This is a systematic review which includes a meta-analysis.

### Data sources and search strategy

Review protocol not exist since, we did not register in Cochran's library. The PRISMA statement for the reporting of systematic reviews recommended by the Cochran Collaboration was followed while conducting this meta-analysis [Additional file 1] [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 internet search from the electronic databases of Pub Med, Google Scholar, web of science and Scopus from Nov. 2-12 2020.

Searches were performed using the search terms under two search themes that were combined using the Boolean operator "AND". For the theme of "Pre-cancerous cervical lesion" a combination of text words was 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 theme of "HIV status", "Positive" and "other population group" was used.

### Eligibility 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 lesion, according to HIV status and (4) Newcastle-Ottawa Scale (NOS) or adapted Newcastle-Ottawa Scale (NOS) score of 5 or greater (5) the studies published from 2015 to 2020.

Studies that not included participants with Pre-cancerous cervical lesion according to HIV status and studies conducted not in Ethiopia were excluded to avoid the combination of studies that were not comparable.

### Data extraction and quality assessment

The data extraction and quality assessment was performed by three

reviewers that were not involved during 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 and definition of PCCL.

All studies conducted multivariable analysis. As a result, variables that were fully adjusted for potential confounding were selected.

Quality assessment was conducted using the ten-star Newcastle Ottawa Quality Assessment Scale (NOS) [18]. We have selected studies with greater than 50% NOS score (Table 1).

Three authors assessed the articles for inclusion in the review (Figure 1). Disagreements between assessors were managed through discussion and majority decisions among the three reviewers.

### Outcome measurement

Visual Inspection of the Cervix with Acetic Acid (*via*): Screening method which involves naked-eye inspection of the uterine cervix 1 min after application of a 3%-5% solution of acetic acid using a cotton swab or a spray [8,19].

PCCL: If a woman with *via* result of raised and thickened white plaques or acetowhite epithelium, usually near the Squamo-Columnar Junction (SCJ) diagnosed as having PCCL and *via* result of smooth, pink, uniform and featureless cervix; cervical ectropion; polyp; cervicitis; inflammation; and/or nabothian cyst after applying a dilute solution of acetic acid is considered as not having 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. Hence, statistical significant publication bias was declared at a p-value less than 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 number of PCCL in HIV positive versus HIV negative. A meta-analysis comparing PCCL between HIV positive and HIV negative in all included studies was performed.

A fixed-effects model was used to estimate the pooled ORs with 95% CIs because 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 P-value <0.05 was considered statistically significant (Figure 1).

## Results

### Study searches and selection

In the initial search, we found a total of 360 records from different electronic search databases which include; 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 3 records were further

excluded by the inclusion and exclusion criteria and 1 excluded by methodological issue. We have selected studies with high NOS score (Table 1). Finally, 9 studies were included for systemic review and meta-

Study	Selection	Comparability	Outcome	NOS scale
Adela.G	****	**	***	10
Assefa.A	****	**	**	9
Dekissesa.Z	****	**	.	8
Derbie.A	****	**	**	9
Geberemariam.A	****	**	***	10
Kassa.R	****	**	**	9
Misgna.K	****	**	***	10
Teka.T	****	**	.	8
Tekalegne.Y	****	**	.	8

Note: Each star represent a high-quality criterion accomplished by the study

Table 1: Newcastle-Ottawa quality assessment scale of included studies in Ethiopia, 2020.

analysis [9-12, 22-26] to estimate the pooled adjusted odds ratio of HIV status with pre-cancerous cervical lesion (Figure 1).

### Characteristics of the studies

These nine studies were published from 2015 to 2020. All the studies included in this review were observational (case-control, cross sectional) studies. A total of 2949 women were included in the analysis. The included studies reported sample size ranging from 164(10) to 528(25) (Table 2).

Of 818(27.7%) HIV positive study participants, 205(25.1%) of them had pre-cancerous cervical lesion. Among 2131(72.3%) HIV negative participants, 433(20.3%) of them have pre-cancerous cervical lesion.

The overall proportion of PCCL was 6.95% and 14.68% among HIV positive and HIV negative respectively (Table 2).

### The association between HIV status and pre-cancerous cervical lesion

The pooled adjusted odds ratios for pre-cancerous cervical lesion

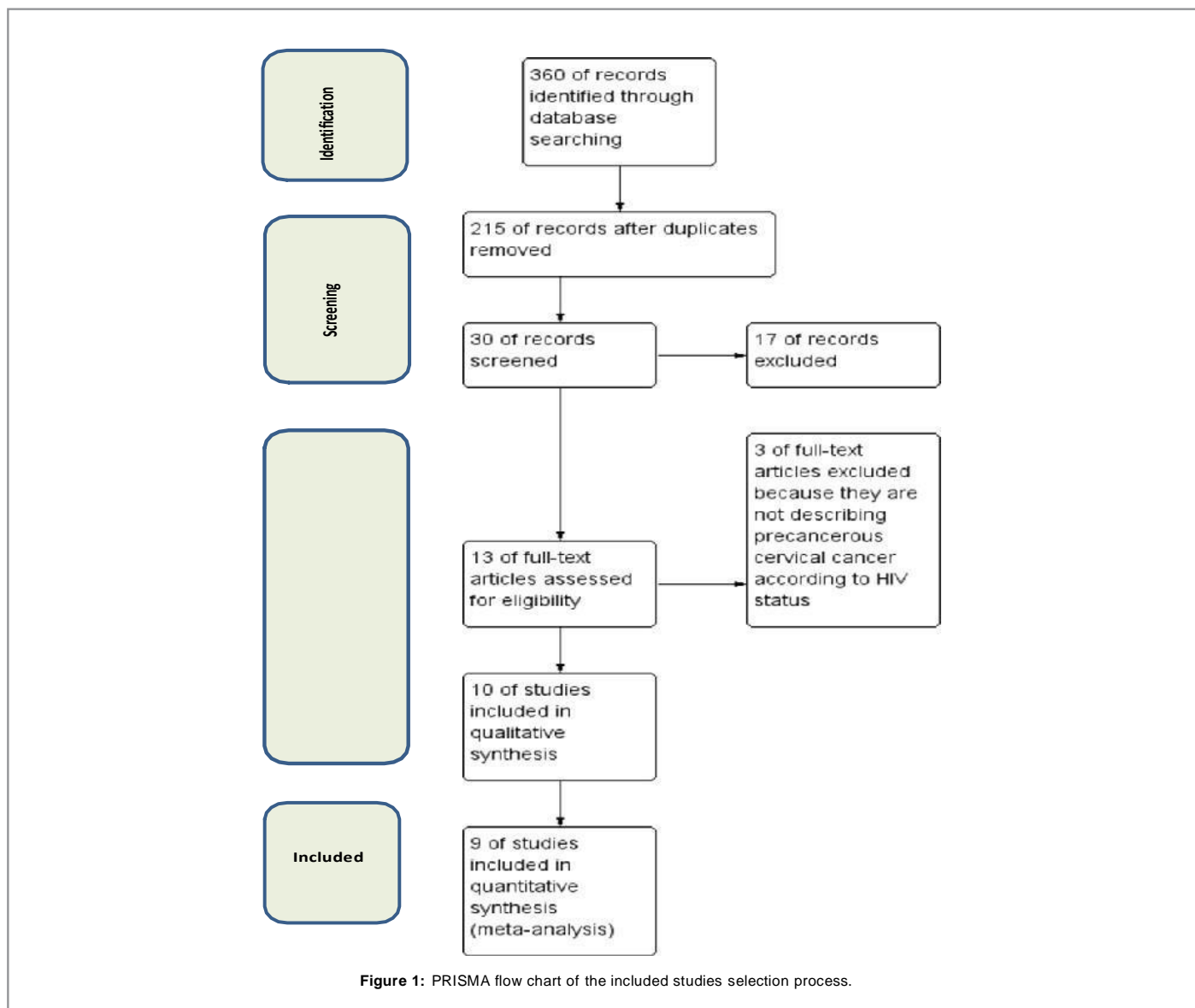


Figure 1: PRISMA flow chart of the included studies selection process.

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 Marko's referral hospital, East Gojjam, North west 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 precancerous 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 precancerous 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 Precervical 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 Precancerous Lesion in Public Hospitals of Oromia Region, Ethiopia: Unmatched Case-Control Study	Positive	26	35	24
			Negative	45	110	

Table 2: Characteristics of studies for HIV infection and pre-cancerous cervical lesion among women in Ethiopia, 2020(n=9).

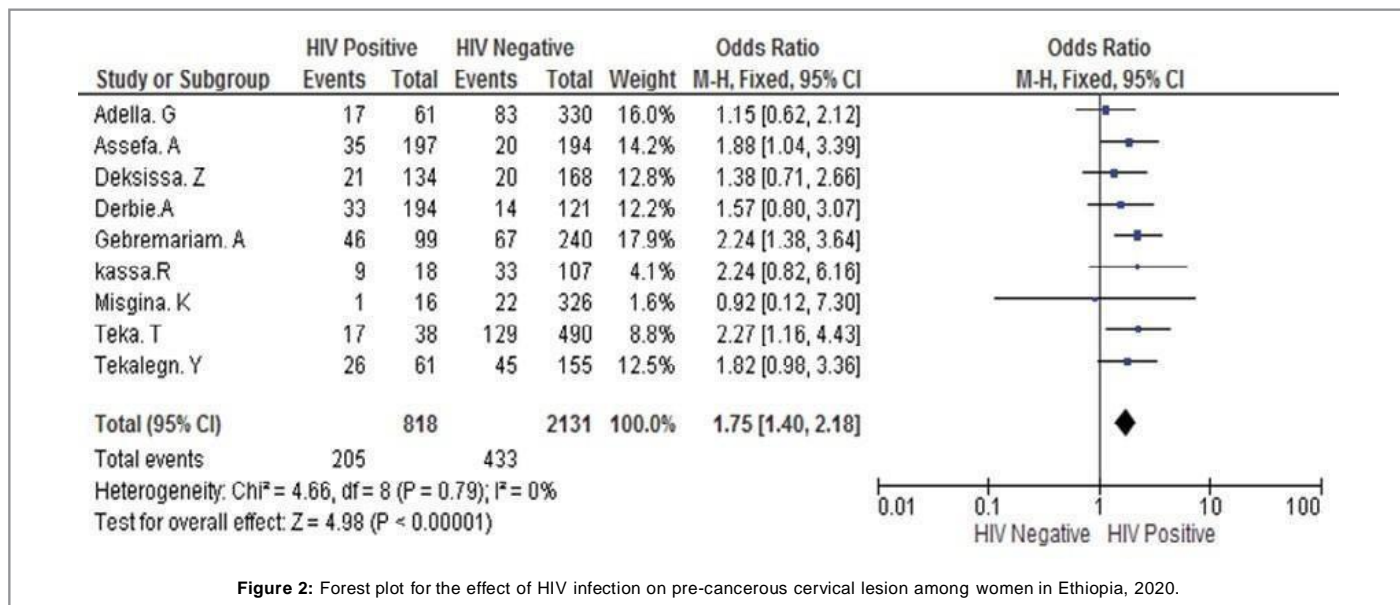


Figure 2: Forest plot for the effect of HIV infection on pre-cancerous cervical lesion among women in Ethiopia, 2020.

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  $P = 0.793$ ) (Figure 2).

We assessed the funnel plot for asymmetry by visual inspection for pre-cancerous cervical lesion and HIV status. No publication bias was observed (Egger's test:  $P = 0.455$ , Begg's test:  $P = 0.532$ ).

## 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 lesion.

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 woman is 1.75 times more likely compared with HIV negative (OR 1.75; 95% CI: 1.40, 2.18,  $P < 10^{-6}$ ,  $I^2 = 0\%$ )

This finding is consistent with several studies conducted in Tanzania [27,28], Swaziland [29], Zimbabwe [30], South Africa [31], Dessie [32] and Yirgalem [33] which show association of HIV and pre-cancerous cervical lesions. The finding of this study is also supported by other studies in Kenya [34] and Senegal [35] which are reporting an increased risk of cervical dysplasia among HIV positive compared to HIV negative women. This could be due to the role of HIV infection on immune system [36]. Additionally, HIV infection was associated with higher incidence and reduced clearance of HPV infection [37].



However, the result of this study was different from the study done in Rwanda [38] and several studies conducted in different parts of Ethiopia (9-12,22-26) where there was no association between HIV status and pre-cancerous cervical lesion among women. These discrepancies could be explained in part by differences in lifestyle factors such as sociocultural characteristics, nutritional, environmental, sexual behaviour and hygiene of study population. The varying associations may also reflect differences in sample size of the studies.

Finally, this study has some limitations. Among them, firstly, in this study cases and controls were identified only *via* their current *via* result; associated with the validity of this screening test, there could be misclassification of cases and controls. This might contribute to underestimating the estimation of cause effect relationship between some of the explanatory variables and the outcome of interest, pre-cancerous cervical lesion. Secondly, 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 small number of included studies.

## Conclusion

Cervical cancer continues to be a public health problem in Ethiopia. The finding of this systematic review suggests a positive association between HIV status and pre-cervical cervical lesion.

Therefore regular screening of HIV-infected women is of paramount importance. The success of any strategy is highly dependent on expanding access to all HIV-infected women, obtaining high follow-up rate from the point of screening. Conducting well-designed prospective cohort study to study natural history pre cervical lesion among HIV infected women in Ethiopia is warranted.

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## Data Availability Statement

All data relevant to the study are included in the article or uploaded as supplementary information. The data for the meta-analyses conducted are included in the study.

## Statement of Ethics

The author has no ethical conflicts to disclose.

## Conflicts of Interest

No support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

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## Authors' Contribution

AAA, KTT and ETT conducted the eligibility screening of shortlisted studies, extracted the data and conducted the analysis with input from all authors. MKT and GAG conducted the initial literature searches. AAA, KTT, ETT GTW and DZB completed the initial drafts

of the manuscript. AAA and KTT reviewed the statistical methods. All authors (AAA, KTT, ETT, MKT, GAG, GTW and DZB) read and approved the final manuscript.

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