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Pooled Prevalence and Associated Factors of Precancerous Cervical Lesion Among Women in Ethiopia

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POOLED PREVALENCE AND ASSOCIATED FACTORS OF PRECANCEROUS CERVICAL LESION AMONG WOMEN IN ETHIOPIA:

A SYSTEMATIC REVIEW AND META-ANALYSIS

PRINCIPAL INVESTIGATOR: DEREJE ZENA (BSc)

A THESIS RESEARCH SUBMITTED TO BAHIR DAR UNIVERSITY COLLEGE OF MEDICINE AND HEALTH SCIENCES, SCHOOL OF PUBLIC HEALTH, DEPARTMENT OF EPIDEMIOLOGY AND BIOSTATISTICS IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF PUBLIC HEALTH IN EPIDEMIOLOGY

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DECLARATION

I DECLARED THAT THIS IS MY ORIGINAL WORK THAT HAS NEVER BEEN PRESENTED IN THIS OR ANY OTHER UNIVERSITY, AND THAT ALL THE RESOURCES AND MATERIALS USED FOR THE RESEARCH HAVE BEEN FULLY ACKNOWLEDGED.

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Acronyms and Abbreviations

AJOL---------African Journal Online

BMC----------BioMed Central

DNA----------Deoxyribonucleic Acid

HIV----------Human Immunodeficiency Virus

HPV----------Human Papilloma Virus

JBI----------Joanna Briggs Institute database

MASARI------Meta-Analysis of Statistics Assessment and Review Instruments

MEDLINE-----Medical Literature Analysis and Retrieval System Online

MOOSE------Methods of Observational Studies in Epidemiology

Popline-------Population Information Online

PRISMA------Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PubMed------Public Medicine

RevMan------Revie Manager

ROBINS-I ---Risk Of Bias In Non-randomized Studies of Interventions

SNNPR-------Southern Nations Nationalities and People Region

SSA----------Sub-Saharan Africa

STI----------Sexual Transmitted Infection

VIA----------Visual Inspection with Acetic acid

WHO----------World Health Organization

WWW--------World Wide Web

Abstract

Background: Cervical cancer remains the most common cancer of women worldwide. Its burden is more serious in the developing countries. It is also the second common deaths of women in Ethiopia followed by breast cancer. Even though, some studies were conducted to assess the prevalence and associated factors of precancerous cervical lesion among women in Ethiopia, a variation in reported prevalence across the studies were observed.

Objective: This study was intended to determine the pooled prevalence and associated factors of precancerous cervical lesion among women in Ethiopia.

Methodology: Published and unpublished articles reported from 2010 to 2019 were systematically searched using a comprehensive search of electronic databases including PubMed, Congress Library, and Web science core collection and Google scholar for grey literature. The methodological qualities of included studies were evaluating using Joanna Briggs Institute meta-Analysis of Statistics Assessment and Review Instruments by two independent review authors. The pooled prevalence estimate was calculated using MedCalc software-version 19.0.7 and the pooled odd ratios for predictors was calculated using RevMan software version 5.3.

Results: The pooled prevalence of precancerous cervical lesion among women in Ethiopia was 13.4%, 95% CI (10.63, 16.37%). Statistically significant heterogeneity between studies was detected (I^2=83.10% ($p<0.0001$). Among all measured associated factors: numbers of women's' life time sexual partners >1, OR=2.50,95% Cl (3.70,4.76), being HIV positive women, OR=2.44,95% CI (1.33,4.61), women having history of STI, OR=1.99,95% CI (1.02,3.87), women's income <1000 birr, OR=1.78,95% CI (1.19,2.65) and women had experience of contraceptive use, OR=2.32, 95% CI (1.75,3.43) were had statistical significant association with precancerous cervical lesion among women in Ethiopia

Conclusion: The pooled prevalence of precancerous cervical lesion among women in Ethiopia was high as compared to the 5-year worldwide cervical cancer prevalence (1). Moreover; there was a variation of cervical cancer reports across studies. Therefore; consistently reporting of this information is important for researchers to enhance future studies and also it is useful for better understanding of cervical cancer burden in Ethiopia by policy makers and practitioners for early prevention, diagnosis, and treatment of the disease.

Keywords: Precancerous cervical lesion, Cervical Cancer; Cancer of the Uterine Cervix; Cervical Neoplasms; Cervix Neoplasms.

1. Introduction

1.1 Background

Cervical cancer is a cancer arising from the cervix. It is due to the abnormal growth of cells and can to spread to other parts of the body. Typically, no symptoms are seen at early stage. Later symptoms may include abnormal vaginal bleeding, pelvic pain, or pain during sexual intercourse (2). It is stated as a major public health problem worldwide. Cervical cancer is a sexually transmitted disease caused by Human papillomavirus (HPV). The most common types of HPV are type 16 and 18 which cause 70% of cervical cancers and precancerous cervical lesion (3).

Precancerous cervical lesion goes through many stages and takes many years to develop into cervical cancer. It becomes cancer when the abnormal cells spread below the epithelial layer down into the deeper tissues of the cervix (3). The most common types of precancerous cervical lesions include a) Atypical squamous cells when abnormalities have been detected in the squamous cells of your cervix, b) Squamous intraepithelial lesion when the lesions have changed and classified as either low-grade or high-grade, with high-grade lesions being more likely to progress to cervical cancer and c) Atypical glandular cells when there is a possible precancerous lesion signal in the upper area of the cervix or inside the uterus (4).

In 2018 cervical cancer is estimated as the fourth most frequent cancer among leading causes of death for women worldwide. It represents 7.5% of all female cancer deaths. More than 85% of these occurred in less developed countries(3).

According to the latest WHO data published in 2017, cervical cancer accounts 0.78% of total deaths in Ethiopia. That is about 1 death due to cervical cancer of every 128 deaths, 14 people die of Cervical Cancer each day or an average of 1 death occurs every 2 hours(5).

A precancerous lesion is preventable through periodic screening and early detection of lesions before progress to cancer. It can be treated easily by cryotherapy using freezing gas (liquid nitrogen), Loop electrosurgical excision procedure, Laser treatment and it is also destroyed with a beam of laser light and Conization. Thus, early treatment of a precancerous cervical lesion can help women avoid getting of cervical cancer (4),(6).

The most frequent method for cervical cancer screening is cytology, and there are alternative methods such as Human Papilloma Virus (HPV) Deoxyribonucleic Acid (DNA) tests, Colposcopy, Cervical biopsy, Endometrial sampling and Visual Inspection with Acetic Acid (VIA). VIA is an alternative to cytology-based screenings in low resource settings. It is the 'see and treat' approach(7).

Low level of awareness, lack of effective screening programs, and lack of attention to women's health are the possible factors that leads to higher the prevalence rate of cervical cancers in the Ethiopia (13.4%). As a result, more than 80% of cervical cancer cases are detected at a late stage due to lack of information and weak preparedness to provide services(8).

Vaccines against HPV 16 and 18 are recommended by WHO and have been approved for use in many countries including Ethiopia(3).

The vaccine is widely administered in rich countries. While countries with the highest burden of cervical cancer in Africa are covering late (9).

Ethiopia launched Human Papilloma Virus (HPV) vaccination pilot project in December 2015 targeting adolescent girls in the 9-13 year age groups in Oromia and Tigray regions(8).

precancerous cervical lesion can be cured if it is diagnosed and treated at an early stage with the alignment of good life styles (9).

1.2. Statement of the problem

One of the major problems that threaten the developing countries is cervical cancer which is a serious threat for the global community. Approximately 311 000 women died with cervical cancer globally in 2018; more than 85% of these deaths occurring in low and middle-income countries (3).

Cervical cancer is the second common cancer deaths of women in Ethiopia followed by breast cancer. About 14 people die of cervical cancer each day or an average of 1 death occurred every 2 hours in 2017(5).

Some studies revealed that low level of awareness, lack of effective screening programs, and insufficient attention to women's health were the possible factors that leads to higher prevalence rate of cervical cancers in the Ethiopia(5).

The common risk factors for cervical cancer include low immune status, co-infection with other sexually transmitted agents, having multiple sexual partners, increased number of children born, early marriage and tobacco smoking (8).

Some considerable efforts like pprovision of education on safe sexual practices, promotion and provision of condoms for those already engaged in sexual activity, warnings about tobacco use, cervical cancer screening and treatment programs have been made by the Ethiopia government and international partners to reduce the prevalence of cervical cancer among women in the country on. However; all these efforts are still unsatisfactory (10).

Even though, some epidemiological studies were available to assess cervical cancer distribution and associated factors among women in Ethiopia. There was a variation of reports on cervical cancer prevalence across different geographical areas in the country. Therefore, the main objective of this study was to determine the pooled prevalence and associated factors of precancerous cervical lesion among women in Ethiopia from 2010 to 2019

1.3. Review of literatures

1.3.1 Prevalence of precancerous cervical lesion among women in Ethiopia

Cervical cancer prevalence varies substantially around the world. The 5-years global prevalence of cervical cancer prevalence was 9% (1). However, it was 21.4% in Eastern Europe, 16.1% in Latin America and 24.0% in Sub-Saharan Africa(11).

Cervical cancer was one of the main causes of death in women in the United States earlier, but the numbers of deaths from cervical cancer were reduced considerably by increasing women's level of awareness on cervical cancer screening programs in the past three decades (1).

In Western Europe the prevalence of HPV ranges from 9.4% to 12.1% across countries (12). While, different studies in different countries show that the overall prevalence of HPV was 15.54% in China (13), 8.1% in Qatari and non-Qatari Arab women (14).

The 5-year prevalence of cervical cancer in Sub-Saharan Africa was 27.6 % with an incidence and mortality rate of 26% and 23% respectively (1). Its prevalence across African countries ranges from 12% to 46%(15).

Among some African countries, the overall prevalence of HPV was 10.4% in Egypt with highest prevalence of 9.2% amongst women aged 45–54 years (16), 3.7% in Ghana (17) and *24% in Sudan (18).*

According to WHO Ethiopian fact sheet, the 5-years prevalence of cervical cancer accounts 19.86% per 100,000 women of all age with an incidence rate of 13.6% (5).

Another study in Ethiopia also showed that the 5-year cervical cancer prevalence and incidence rate was 18% with a mortality rate of 17%(1). The prevalence of cervical cancer was varied in different parts of the country. The prevalence of VIA positive lesions was 12.9 % in Jimma (19), 14.1 % in Debre Markos (20), 16.5% in Yirgalem (21), 22.1% in Southern Ethiopia (22), 20.1% in Amhara Region (23), 13.7% in Addis Ababa (24), 5.9% (15) and 17.3% in different parts of the rural Ethiopia (25). Moreover; other researchers reported the prevalence of cervical cancer as it was 39.5% (26) in higher gynecological clinics of Ethiopia and 6.7% in Northern Ethiopia(27)

1.3.2 Associated factors of precancerous cervical lesion among women in Ethiopia

Different study findings showed that some socio-demographic variables and associated factors like age, educational level, marital status, sexual behavior with multiple partners, cigarette smoking and Health seeking behavior appears as prominent predictor of cervical cancer distribution among women in the country (10)), ((21), (22), (28), (29), (30), (31), (32), (33), (34).

The risk of developing cervical cancer increases with age. More than 20% of cervical cancer cases were observed in women above age 60 years(1).

Cervical cancer was also most frequently diagnosed in women between the ages of 35 and 44 years(1) but the prevalence of HPV in Egypt was highest (9.2%) among women aged 45–54 years(16).

Even though, majority of the respondents had heard about cervical cancer, only 31.0% of the respondents had have above-average knowledge to utilizes the services in Ethiopia (31).

The proportion of women who had ever been screened was significantly higher among those who demonstrated positive attitude to cervical cancer screening (81.5%). Whereas; those who had negative attitude had 63% lesser odds of being screened as compared those who had a positive attitude to cervical cancer screening.

A study conducted among women in Bangladesh & Nigeria in 2014 revealed that 12% (29) and 47.1% of the respondents had a good knowledge on cervical cancer services but in Nigeria only 39.5% of them knew something about Pap smear (35).

Lack of awareness and health seeking behavior on cervical cancer was common among women residing in developing countries (36, 37). Only 14.2 % study participants have shown a health seeking behavior on cervical cancer services in Ethiopia((30), (34))

1.4. Conceptual framework

Determinants of precancerous cervical lesion among women in Ethiopia

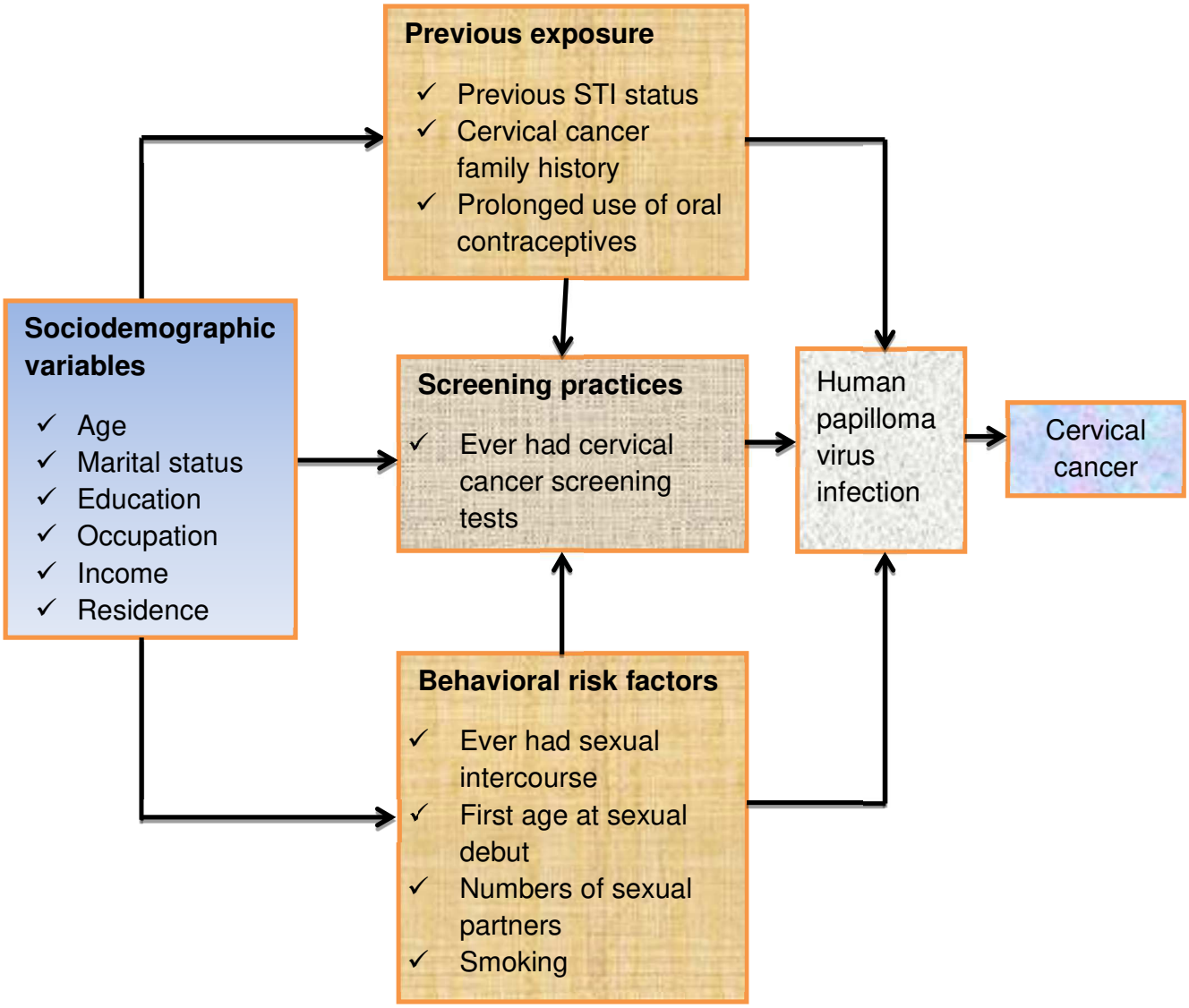

Figure 1: Determinants of precancerous cervical lesion among women in Ethiopia.

1.5. Justification of the study

So, understanding of cervical cancer prevalence and its associated factors was very crucial to improve the health of Ethiopian women through comprehensive and integrated cervical cancer control programs including: vaccination against HPV, cervical cancer screening and treatment of pre-cancerous lesions, diagnosis and treatment of invasive cervical cancer and palliative cares.

Therefore, this study was primarily intended to estimate pooled prevalence of precancerous cervical lesion and assess its associated factors among women in Ethiopia from 2010 to 2019.

Moreover; this study was conducted

- To answer questions not posed by the individual studies.
- To settle controversies arising from apparently conflicting studies or
- To improve the precision for better prediction of the overall effect estimates
- To generate new hypotheses

This study can also serve as a baseline for any high scale study to be done on precancerous cervical lesion prevalence and associated factors at the national level.

2. Objectives

2.1. General objective

The main objective of this study was to generate local evidence on the pooled prevalence and associated factors of precancerous cervical lesion among women in Ethiopia from 2010 to 2019.

2.2. Specific objective:

- ✓ To estimate the pooled prevalence of precancerous cervical lesion among women in Ethiopia from 2010 to 2019
- ✓ To identify associated factors of precancerous cervical lesion among women in Ethiopia from 2010 to 2019

3. Methods and materials

3.1. Study design and setting

Health facility-based studies conducted on precancerous cervical lesion among women in Ethiopian from 2010 to 2019 were used for this systemic review and meta-analysis project work. Ethiopia is one of the east African countries situated in the horn of Africa having a total population of 109,616,652 and 50.2% of the female population, 56.2 years (53.6-men, 58.8-women) of Life expectancy and 49.1 % of Literacy. The landmark of Ethiopia covers an area of1,104,300KM^2(3). The country has a federal system of governance with nine regional states and two chartered cities (32).

3.2. Population, Intervention, comparator and Outcomes (PICOs)

Table 1: The Population, Intervention, Comparator and Outcomes (PICOs) for associated factors of precancerous cervical lesion among women in Ethiopia from 2010 -2019

Intervention/Exposure	comparator	Outcomes	Population
Education	Primarily and above education	Cervical cancer positive	Women in Ethiopia
Married, Divorced & Widowed	Single	Cervical cancer positive	Women in Ethiopia
Women having multiple sexual partners	Women did not have multiple sexual partners	Cervical cancer positive	Women in Ethiopia
First intercourse <15 years	First intercourse ≥15 years	Cervical cancer positive	Women in Ethiopia
Women having previous history of STI infection	Women did not have previous history of STI infection	Cervical cancer positive	Women in Ethiopia

3.3. Searching strategy

The presence of systemic review and meta-analysis on the pooled prevalence and associated factors of precancerous cervical lesion among women in Ethiopia was checked by searching different databases like PubMed, Google scholar, Joanna Briggs Institute databases (JBI), the national health center review and dissemination databases, and Prospero. As far as we searched, there was no systematic review conducted on our topic of interest. Thus, the actual search was conducted from August 1 to 30, 2019 by using comprehensive electronic databases like PubMed, Congress Library, Medline(TR), Web science core collection for the published work and Google scholar for grey literature using Mesh terms "Prevalence OR Frequency OR Occurrence AND Risk Factors AND Cancer of Cervix OR Cancer of the Cervix OR Cervical OR Cancer of the Uterine Cervix OR Uterine Cervical Cancer OR Cervical Intraepithelial Neoplasia OR Cervical Cancer OR Cervix Cancer OR Cervical Neoplasms OR Uterine Cervical Neoplasms OR Cervix Neoplasms OR Neoplasms OR Cervix OR Uterine Cervical Cancer OR Tumor of the Uterine Cervix OR Uterine Cervical Dysplasia AND Girls OR Woman OR Women's Groups AND Ethiopia".

3.4. Inclusion criteria

The inclusion criteria's for this study were

- *Study designs*: all observational studies conducted at a health facility level to assess the prevalence or associated factors of precancerous cervical lesion among women residing in Ethiopia,
- *Publication status*: those published articles or grey literature reported from 2010 to 2019,
- *Language:* articles reported with the English language,
- *Study quality*: those primary studies scored ≥60% of the Joanna Briggs Institute (JBI) criteria's for assessing the quality of primary studies were included in the meta-analysis and
- *The outcome of interest*: precancerous cervical lesion positive result diagnosed by any methods

3.5. Data extraction

The retrieved data were screened independently by two reviewer authors (DZ and BE) to verify studies that possibly meet inclusion criteria. Any disagreement was resolved through discussion with a third reviewer (KM.). The third reviewer mediated any issues that remained unresolved. Data were extracted based on standardizing data extraction tools adapted from the JBI Meta-Analysis of Statistics Assessment and Review Instruments (MASARI) (38). Appropriate critical appraisal checklist of Meta-analysis of Observational Studies in Epidemiology (MOOSE) for systematic reviews (39) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting systematic reviews and meta-analyses were used to assess the overall methodological quality of included studies(40). EndNote X5 citation manager was used to import and handle all searched articles and remove duplicates. Each study data was extracted following study characteristics (year of publication, women demographics and baseline characteristics, study setting, number of cases enrolled, study population, and study designs), prevalence and associated factors of precancerous cervical lesion. The data were extracted from the included studies independently by the two authors and the completeness of the retrieved data was checked by the two authors together.

Table 2: Summary of eligible articles included to review the pooled prevalence and associated factors of precancerous cervical lesion among women in in Ethiopia.

No	ID	Author name and publication	Tittle of the study	Study design	Overall quality
1	10	**Mesele B. etal, 2015**	**Risk Factors Associated with Invasive Cervical Carcinoma among Women Attending Jimma University Specialized Hospital, Southwest Ethiopia**	**Case control**	**8/10**
2	16	**Deksissa etal, 2015**	**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**	**Cross-sectional**	**7/9**
3	35	**Getinet M. etal, 2015**	**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**	**Comparative Cross-sectional**	**6/8**
4	47	**Kassa R. 2018**	**Risk factors associated with precancerous cervical lesion among women screened at Marie Stops Ethiopia, Adama town, Ethiopia**	**Case control**	**8/10**
5	50	**Leyh-B. etal, 2014**	**Cervical human papillomavirus prevalence and genotype distribution among hybrid capture 2 positive women 15 to 64 years of age in the Gurage zone, rural Ethiopia**	**Cross-sectional**	**7/8**
6	61	**Gebreheat G. etal, 2018**	**Factors associated with cervical precancerous lesions among women screened for cervical cancer in Addis Ababa, Ethiopia**	**Case control**	**8/10**
7	69	**HailemariamT.etal,2017**	**Prevalence of Cervical Cancer and Associated Risk Factors among Women Attending Cervical Cancer Screening and Diagnosis Center at Yirgalem General Hospital, Southern Ethiopia**	**Cross-sectional**	**7/9**
8	76	**Misgina etal,2016**	**Prevalence of precancerous cervical lesion and associated factors among women in North Ethiopia**	**Cross-sectional**	**7/9**
9	85	**Ali etal, 2019**	**Burden and genotype distribution of high-risk Human Papillomavirus infection and cervical cytology abnormalities at selected obstetrics and gynecology clinics of Addis Ababa, Ethiopia**	**Cross-sectional**	**7/9**

Table 3: Summary of eligible articles included to review the pooled prevalence and associated factors of precancerous cervical lesion among women in in Ethiopia.

No	ID	Author name and publication	Total sample size	Prevalence	Statistically significant associated factors
1	10	Mesele B. etal, 2015	180 (60:120)	NA	Women: • 40-59 years, AOR= 4.7 & 95%CI (2.3, 9.6) • Had >1 husband, AOR= 2.0; 95%CI (1.0, 3.9) and • Had > 4 children, AOR =10.3, 95% CI (3.6, 29.0)
2	16	Deksissa etal, 2015	334	43 (12.9%)	• Sexual intercourse < 16 years, OR=2.2,95% CI (1.1, 4.3)
3	35	Getinet M. etal, 2015	391	55 (14.1%)	• HIV+ women, AOR =1.9, 95 % CI (1.1, 3.4) • Multiple sexual partnership, AOR =3.2, 95 % CI (1.1, 10.0) • First sexual contact <15 years, AOR =5.2, 95 % CI (1.5, 17.9) and • Long term oral contraceptive pills use, AOR =11.9, 95% CI (2.1, 16.7)
4	47	Kassa R. 2018	164 (55:109)	NA	• Use of oral contraception OR=2.342, 95CI (1.1, 4.9) • History of STI, A OR= 2.485, 95CI (1.19 5.2) and • Age at1st sexual intercourse <15 years, AOR=6.70, 95CI % (1.73, 10.12)
5	50	Leyh-B. etal, 2014	537	86 (16.1%)	• Widowed AOR =1.85, 95%CI (1.0, 3.4) and • Had >1 lifetime sexual partners AOR =1.83, 95%CI (1.0, 3.2)
6	61	Gebreheat G. etal, 2018	343 (114:229)	NA	• 40–49 years, AOR=2.55, 95% CI (1.5, 4.2) • having history STI AOR=3.20, 95% CI (1.2, 8.1) and • had >/=2 lifetime sexual partners, AOR=2.17, 95% CI (1.0, 4.7)
7	69	HailemariamT.etal,2017	1945	321 (16.5%)	• With HIV, AOR=9.03, 95%CI (4.5, 18.0), • had history of STI, AOR=8.36:95% CI (5.6, 12.4) and • age at first sexual intercourse, AOR=8.97,95%CI (5.6, 14.4)
8	76	Misgina etal,2016	342	23 (6.7%)	
9	85	Ali etal, 2019	366	50 (13.7%)	• Unemployed AOR=9.17, 95%CI (1.6, 52.2) • Positive AOR=5.73, 95%CI (1.1,30.9) and • Resided out of Addis Ababa AOR=8.12, 95%CI (1.1, 57.9)

3.6. Risk of bias (quality) assessment

Two review authors (DZ & BE) were assessing the methodological quality primarily studies independently using appropriate critical appraisal checklist of Meta-analysis of Observational Studies in Epidemiology (MOOSE) before eligible articles were included. Moreover, the completeness of outcome data and other sources of bias were effectively assessed by two review authors (DZ& BE) using Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) with detailed guidance to make domain-level judgments about risk of bias (41). Any disagreements between two review authors (DZ & BE) were resolved by discussion and involvement of a third review author as the mediator (KM). To minimize time-lag bias, the search was updated on August 30, 2019. Those primary studies (which had a score of one point each) was scored ≥60% of the Joanna Briggs Institute (JBI) criteria were included in the meta-analysis. During our study methodological quality assessment and scoring, one disagreement (1/9) has happened between the primary (DZ) and secondary (BE) review authors. But the difference was resolved by the third review author (KM) through discussion. Moreover, a funnel plot was used to assess publication bias.

3.7. Strategy for data synthesis

In total, nine studies were eligible to extract data using a Microsoft excel spread sheet and were presented in terms of authors' name and publication date, sample size, cervical cancer prevalence and other study characteristics. But not all researchers had used the same classification for each predictor at their study level. When this kind of event happened, a better inclusive classification system or category was selected. But for age categories, midpoint calculation was employed to fit it in the best placement. If all these efforts did not work, studies containing unfitted categories for predictors would not be included in the study. Therefore, five cross-sectional, one comparative cross-sectional and three case-control full-text articles conducted at the health facility level reported from 2010 to 2019 were used. Only six full-text articles were used to measure the pooled prevalence of precancerous cervical lesion screened by any methods whereas all nine included full-text articles were chosen to measure associated factors of precancerous cervical lesion among women in Ethiopia. Finally, summary results were presented using tables.

3.8. Data analysis

For this study, 2×2 tables summarizing was computed for each outcome measure. We also calculated a weighted study effect using a fixed effect model or a random-effects model in case of heterogeneity at $P \leq 0.05$ and the χ^2 test at $P \leq 0.10$ significance level during meta-analysis. The pooled prevalence estimate was calculated using MedCalc software-version 19.0.7 whereas the overall effects estimate of odd ratios for associated factors were calculated using RevMan software version 5.3.(42). The variance of the study was stabilized with a Mantel-Haenszel variance random-effects model before pooling the data within a random-effects or fixed-effect meta-analysis model (43). In addition to these, the Funnel plot was used to assess the presence of publication bias (44). Moreover, heterogeneity was evaluated using the χ^2 test and $\mathbf{I^2}$ value(45).

4. Results

4.1. Search results

A total of 124 articles were retrieved and screened. After removing 27 duplicates 97 articles were screened by title and abstract. 80 articles were excluded by unrelated tittle and one article was excluded by poor abstract contents. Then 16 full-text articles were assessed for eligibility, but seven full-text articles were excluded with reason through a critical review process. Finally, a total of nine full-text articles (five Cross-sectional, one Comparative Cross-sectional and three Case-control studies) were met the inclusion criteria and included for this study.

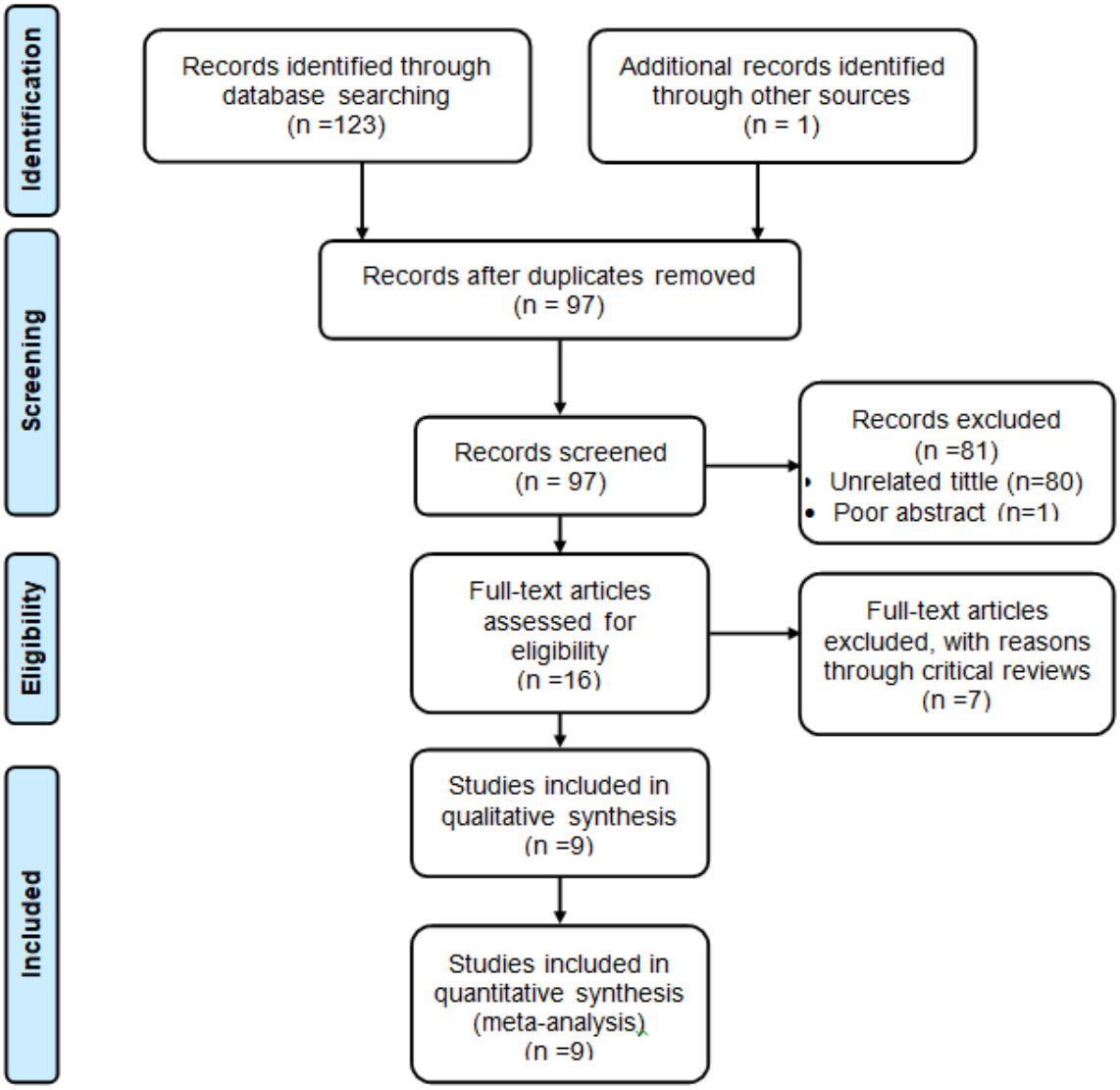

Figure 2: Flow diagram of included and excluded articles to review the prevalence and associated factors of precancerous cervical lesion among women in Ethiopia.

4.2. The pooled prevalence estimates of precancerous cervical lesion among women in Ethiopia

Six full-text articles conducted at health the facility level with a total sample size of 3915 were included to compute the pooled prevalence estimate of precancerous cervical lesion among women in Ethiopia. Therefore, the highest prevalence was observed in a study done in southern Ethiopia (16.5 %) (21). Whereas the lowest point estimate was observed at a study conducted in northern Ethiopia in 2017(6.7%)(27). Statistically significant heterogeneity between studies was also detected (I^2=83.10% (p<0.0001). Due to the combined studies were less than ten, this heterogeneity cannot be explained without running a meta-regression (Table 4).

Table 4: Eligible studies included to estimation the pooled prevalence of precancerous cervical lesion among women in Ethiopia

Study	Sample size	Proportion (%)	95% CI	Weight (%)	
				Fixed	Random
Ali etal 2019	366	13.661	10.31-17.61	9.36	15.90
Deksissa etal 2015	334	12.874	9.48-16.95	8.54	15.55
Getinet M etal 2015	391	14.066	10.78-17.91	10.00	16.14
HailemariamT.etal 2017	1945	16.504	14.88-18.23	49.63	19.61
Leyh B. etal 2014	537	16.015	13.01-19.39	13.72	17.17
Misgana. etal 2016	342	6.725	4.31-9.92	8.75	15.64
Total (fixed effects)	**3915**	**14.676**	**13.58-15.82**	**100.00**	**100.00**
Total (random effects)	**3915**	**13.369**	**10.63-16.37**	**100.00**	**100.00**

Test for heterogeneity

Q	29.5833
DF	5
Significance level	P < 0.0001
I^2 (inconsistency)	83.10%
95% CI for I2	64.48 to 91.96

This study based meta-analysis forest plot with random effects model discovered that more weight was given for a study conducted in Yirgalem General Hospital in 2017(21). As a result, studies given the higher weights were had more influence to predict the pooled effect estimate. Therefore; the combined point estimate of precancerous cervical lesion was found to be 13.4%, 95%CI (10.63, 16.37%) (Figure 3)

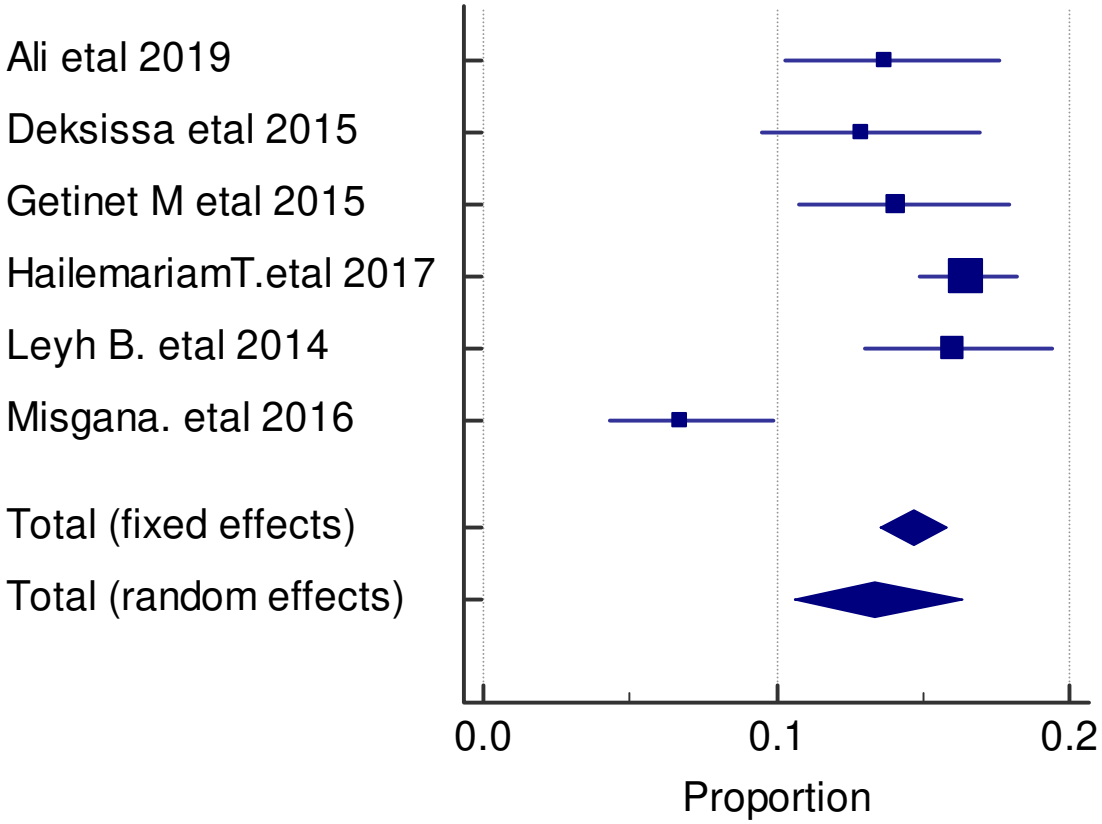

Figure 3: A forest plot showing the pooled prevalence of precancerous cervical lesion among women in Ethiopia.

Publication bias had been indicated by funnel plot asymmetry. This visual inspection of the funnel plot confirmed that the plot was asymmetrical (Figure 4).

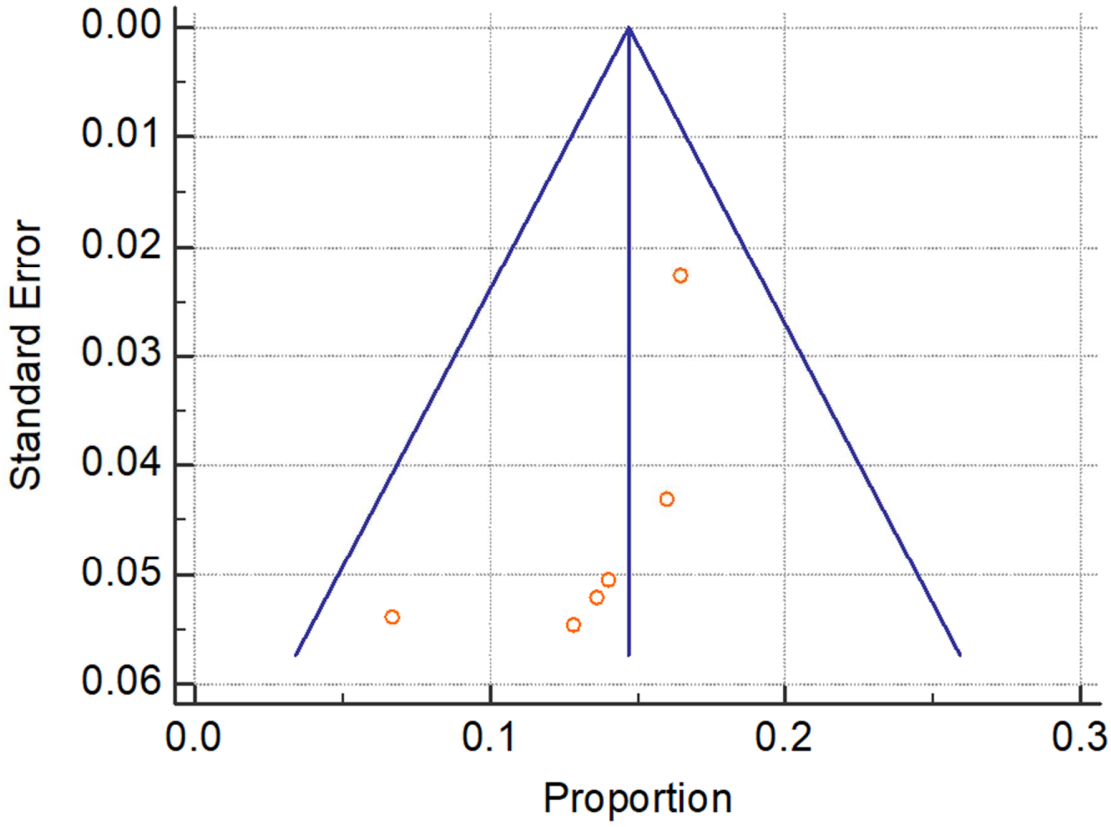

Figure 4: Publication bias among studies conducted on prevalence of precancerous cervical lesion in Ethiopia

4.3. Factors associated with precancerous cervical lesion among women in Ethiopia

All nine eligible full-text reticles were used to access associated factors of precancerous cervical lesion among women in Ethiopia. Of which thee studies were conducted in the Oromia region followed by two studies were conducted in Southern Nations Nationalities and People Region and Addis Ababa and one study each was conducted in Amhara and Tigray regions.

Table 5: Socio-Demographic and other variables associated with precancerous cervical lesion among women in Ethiopia

Articles	Experiment		Control	
	Positive	Total	Positive	Total
Age: (n=6)	≥ 40 years		vs < 40 years	
1. Ali etal, 2019	28	313	10	53
2. Deksissa etal, 2015	2	22	41	308
3. Gebreheat G. etal, 2018	70	154	43	188
4. Kassa R. 2018	6	17	48	144
5. Leyh B. etal, 2014	53	322	33	212
6. Melese B. etal, 2015	44	80	16	100
Education: (n=3)	Non formal educated vs		Literate	
1. Ali etal, 2019	1	38	37	290
2. HailemariamT.etal, 2017	28	40	76	289
3. Kassa R. 2018	3	14	52	96
Marital status: (n=3)	Married	vs	Single	
1. Ali etal, 2019	28	287	7	32
2. HailemariamT.etal, 2017	232	1459	45	89
3. Misgina etal, 2016	19	233	4	109
Marital status: (n=2)	Divorced / widowed	vs	Single	
1. Ali etal, 2019	3	47	7	32
2. HailemariamT.etal, 2017	44	399	45	89
Occupation:(n=3)	Unemployed	vs	Employed	
1. Ali etal, 2019	4	14	34	356
2. Gebreheat G. etal, 2018	83	228	31	115
3. HailemariamT.etal, 2017	65	839	256	1106
Residence:(n=2)	Urban	vs	Rural	
1. HailemariamT.etal, 2017	256	1210	65	735
2. Melese B. etal, 2015	15	54	45	126
Income:(n=2)	<1000 Birr	vs	≥ 1000 Birr	
1. Gebreheat G. etal, 2018	34	80	80	263
2. Melese B. etal, 2015	37	90	23	86
Previous history of STI: (n=6)	Yes	vs	No	
1. Deksissa etal, 2015	8	50	35	280
2. Gebreheat G. etal, 2018	39	62	75	281
3. Kassa R. 2018	21	45	33	118
4. Leyh B. etal, 2014	11	26	73	511
5. Melese B. etal, 2015	5	27	55	153
6. Misgina etal,2016	8	82	15	260
Ever had cervical cancer screening:(n=2)	Yes	vs	No	
1. Gebreheat G. etal, 2018	87	276	28	68
2. Melese B. etal, 2015	58	171	2	9

Table 6: Socio-Demographic and other variables associated with precancerous cervical lesion among women in Ethiopia (continued)

Articles	Experiment		Control	
	Positive	Total	Positive	Total
Ever use modern Contraceptives:(n=3)	Yes	vs	No	
1. Deksissa etal, 2015	18	111	25	219
2. HailemariamT.etal, 2017	274	1487	108	1477
3. Kassa R. 2018	41	102	14	59
HIV status: (n=6)	Positive	vs	Negative	
1. Deksissa etal, 2015	21	134	20	168
2. Gebreheat G. etal, 2018	46	99	67	240
3. Getinet M. etal, 2015	35	181	20	194
4. HailemariamT.Etal, 2017	39	65	282	1844
5. Kassa R. 2018	9	18	33	67
6. Misgina etal,2016	1	16	22	326
Age at 1st sexual intercourse: (n=6)	<15-year	vs	≥ 15 years	
1. Ali etal, 2019	2	39	38	327
2. Deksissa etal, 2015	22	144	17	175
3. GebreheatG.etal, 2018	26	70	88	286
4. Kassa R. 2018	25	45	30	119
5. Leyh B. etal, 2014	55	414	31	123
6. Melese B. etal, 2015	6	34	54	146
No of Life time sexual partners: (n=4)	> 1	vs	1	
1. Deksissa etal, 2015	32	241	11	89
2. Gebreheat G. etal, 2018	43	202	71	141
3. Kassa R. 2018	15	81	40	83
4. Melese B. etal, 2015	36	128	24	49

From this subgroup meta-analysis, the study done at Yirgalem General Hospital in 2017 had more effect size and weight to predict the overall effect estimate(21). Its 95% confidence interval did not overlap the line of no effect (null value). The 95% confidence intervals of all other studies overlap 1 (null value). But the 95% CI of the overall effect estimate did overlap not the line of no effect (null value) (Figure 5).

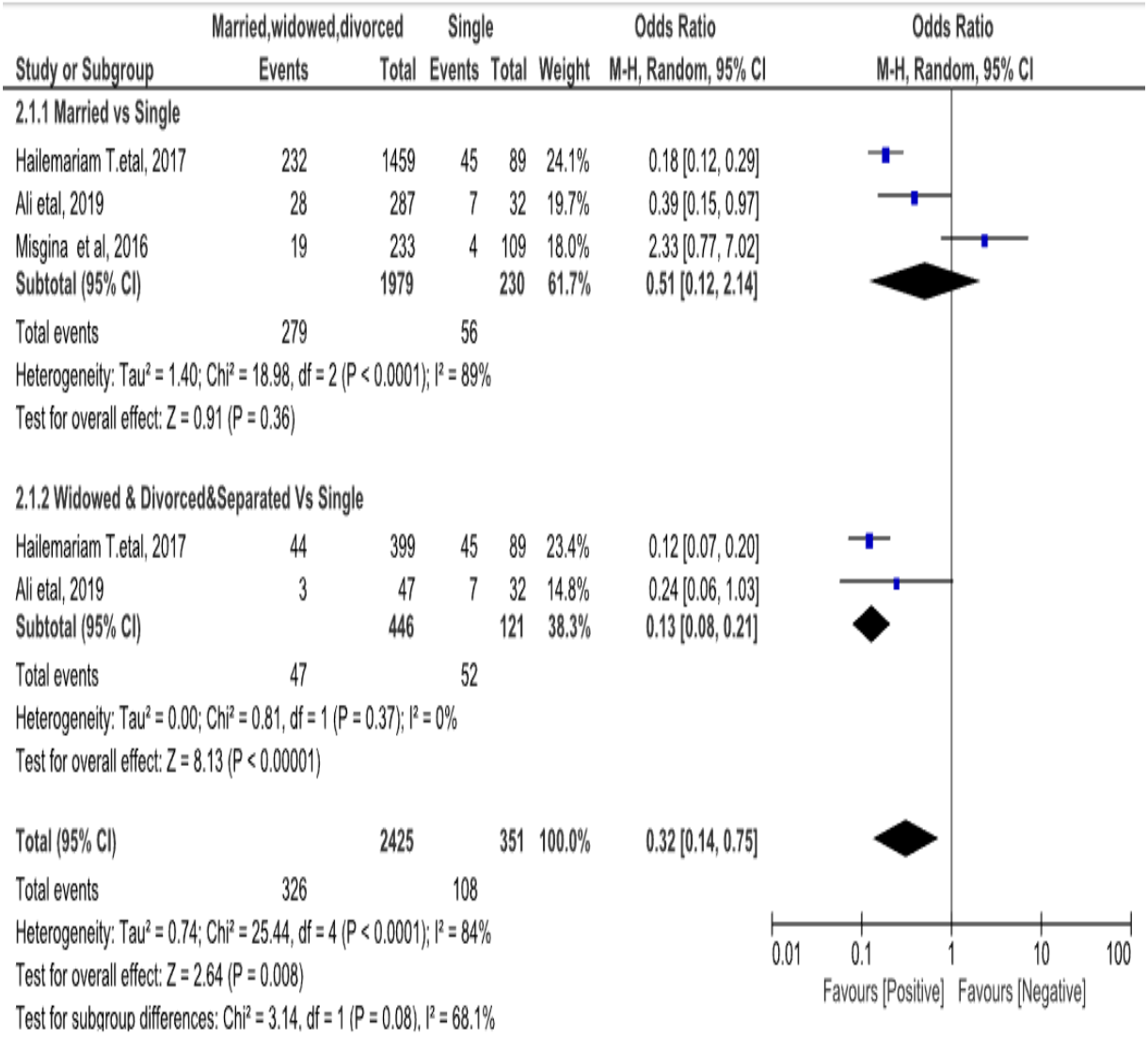

Figure 5: The association between marital status and precancerous cervical lesion among women in Ethiopia

A study conducted in Addis Ababa in 2019 (24) had more effect size to pull the overall effect estimate to the left (favors to the bad event). The 95% CI of this study did not overlap the line of no effect (null value) like a study conducted in Addis Ababa (46) and Jimma (47) in which both had the lowest effect to predict the overall effect estimate (OR=1.34, 95% CI (0.56, 3.12) respectively. More weight (19.2%) was given for studies conducted in Addis Ababa (46) and the Gurage zone(48). Therefore, the overall effect estimates of women's age were OR=1.43, 95 %CI (0.65, 3.12) (Figure 6).

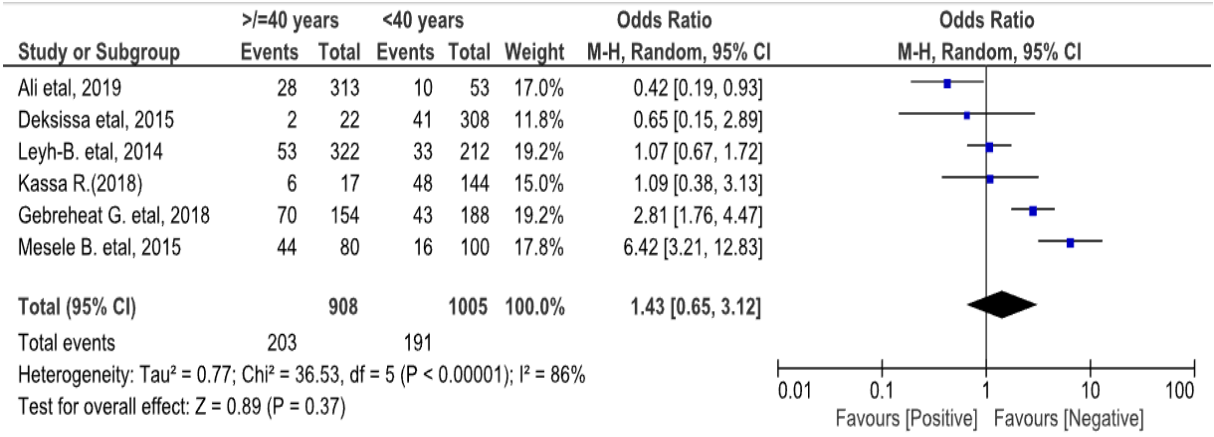

Figure 6: The association between age and precancerous cervical lesion among women in Ethiopia (n=6)

Except for one study(21), all other studies The 95%CI overlap the line of no effect at a study level (24, 46, 49). As a result, the overall effect estimate touches the line of no effect (Figure 7).

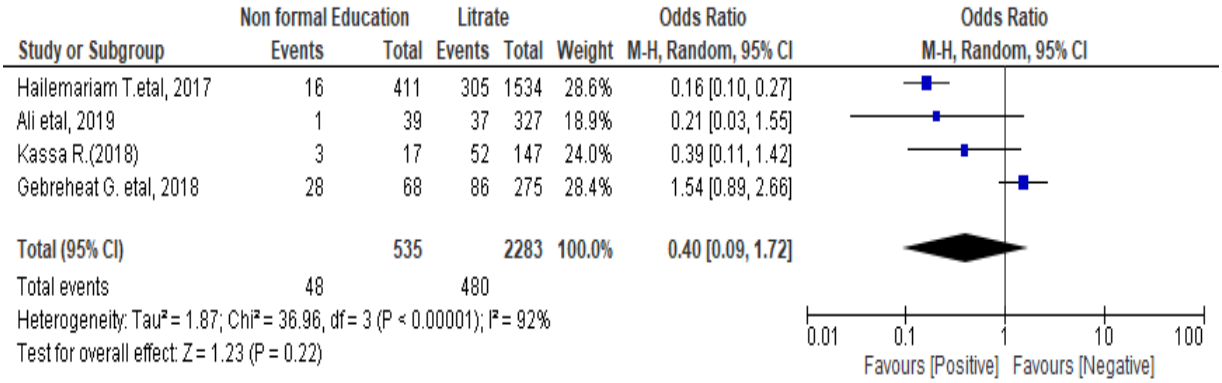

Figure 7: The association between educational background and precancerous cervical lesion among women in Ethiopia (n=4)

The study conducted at Yirgalem General Hospital in 2017 had more effect size and highest weight to forecast the overall effect estimate (21). But a study conducted in Addis Ababa in 2018 had the lowest effect size and weight (24). Due to its higher weight (35.8%) and more effect size, a study done at Yirgalem General Hospital pulls the overall effect estimate towards the better event (favors to negative)(21). Therefore, the 95%CI of the overall effect estimate did overlap the line of no effect (null value) (Figure 8).

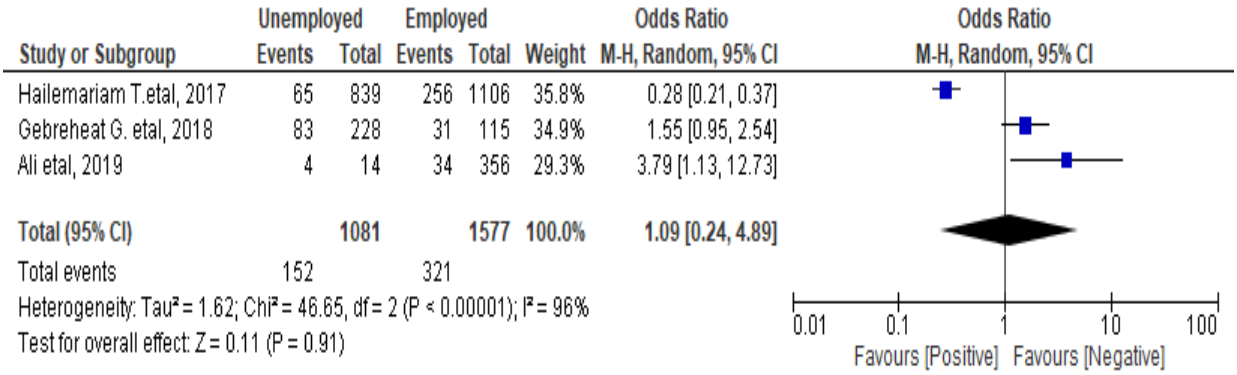

Figure 8: The association between occupation and precancerous cervical lesion among women in Ethiopia (n=3)

In this analysis, more effect size was observed at a study conducted in Jimma (47) whereas more weight (52.7%) was given for a study conducted at Yirgalem General Hospital(21). However, the 95% CI of overall effect estimate, OR=1.44, 95% CI (0.37, 5.58) overlaps the line of no effect (null value) (Figure 9).

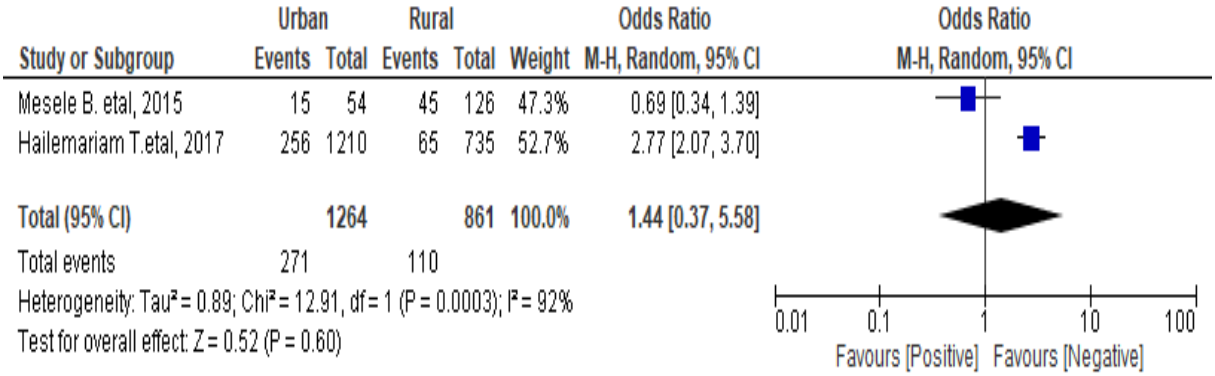

Figure 9: The association between residence and precancerous cervical lesion among women in Ethiopia (n=2)

Income was another important variable to predict precancerous cervical lesion distribution among women in Ethiopia. The 95% confidence intervals of all the studies did not overlap the line of no effect (null value) and the 95% confidence intervals of the overall effect estimate did not overlap the line of no effect (null value) (Figure10).

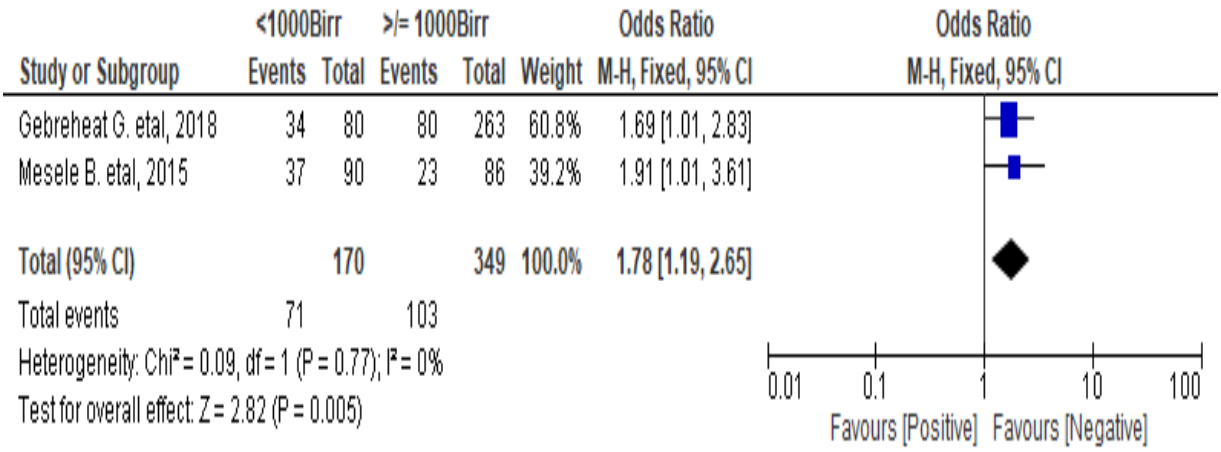

Figure10: The association between income and precancerous cervical lesion among women in Ethiopia (n=2)

As the forest plot indicates that the overall effect estimate did not touch the no effect line or null value even though one study crosses the line of no effect (null value) (Figure11).

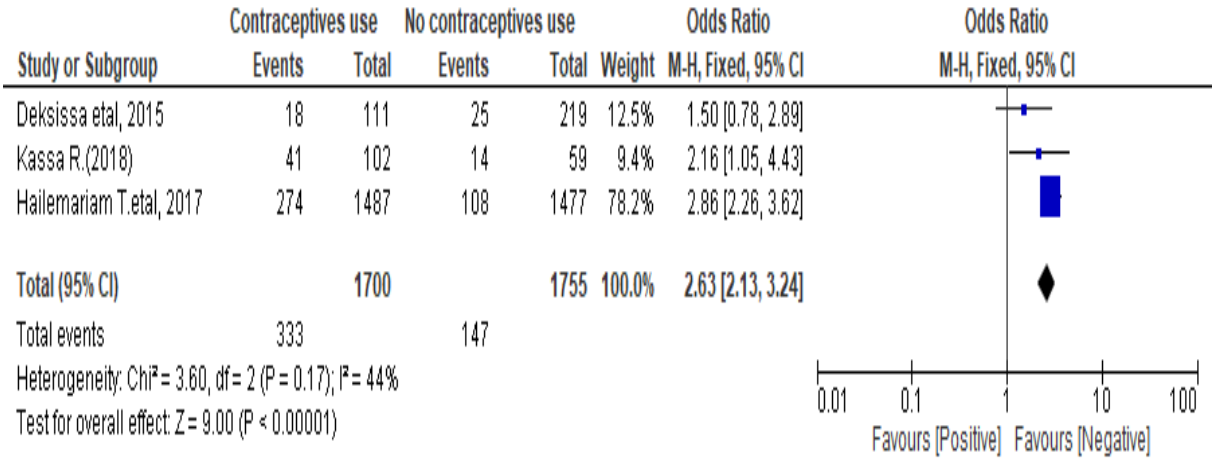

Figure 11: The association between contraceptive use and precancerous cervical lesion among women in Ethiopia (n=3)

All studies except one study done in Jimma (50), the 95% confidence intervals did not touch the line of no effect (null value) (46, 47, 49). As a result, their combined effect pulls the overall effect estimate towards the left (bad event/cervical cancer episode). Thus, the overall pooled prevalence estimates of precancerous cervical lesion prevalence between women having >1-lifetime sexual partners and women had 1-lifetime sexual partner was OR=0.40, 95%CI (021, 0.75) (Figure 12).

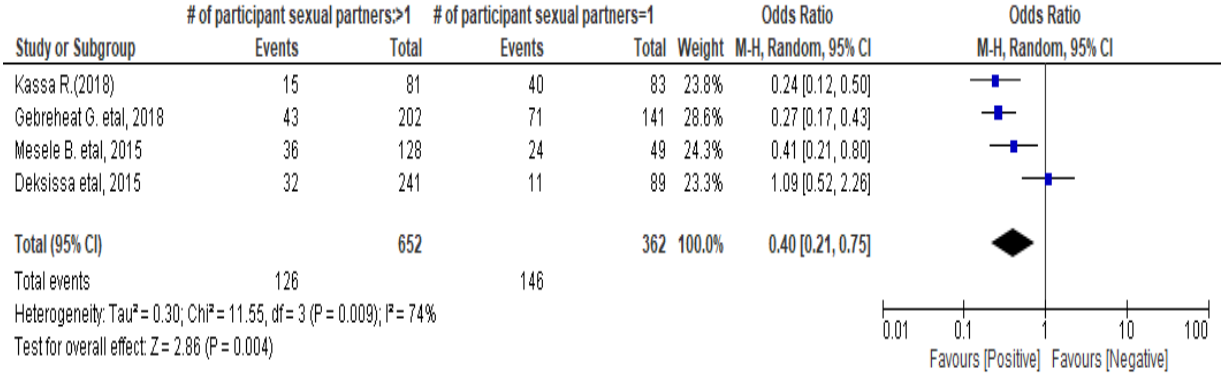

Figure 12: The association between residence and precancerous cervical lesion among women in Ethiopia (n=4)

Like other variables, having a previous history of STI can predict the prevalence of precancerous cervical lesion among women in Ethiopia. The overall effect estimates of cervical cancer between a history of STI and precancerous cervical lesion among women was OR=1.99, 95% CI (1.02, 3.87) (Figure13).

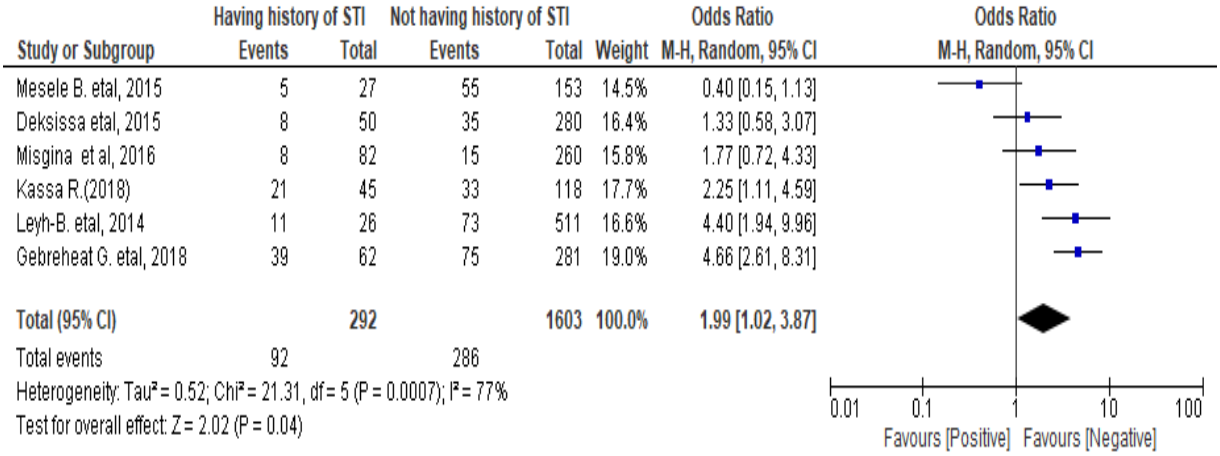

Figure 13: The association between history of STI and precancerous cervical lesion among women in Ethiopia (n=6)

This forest plot shows that the highest effect size but the least weight (7.4%) was given for a study done in North Ethiopia (27). The 95% confidence intervals of studies conducted at Debre Markos referral hospital, Addis Ababa and Yirgalem General Hospital did not overlap the line of no effect (null value) (21, 46, 51) like the pooled prevalence estimate of precancerous cervical lesion between HIV plosive and negative women (Figure 14).

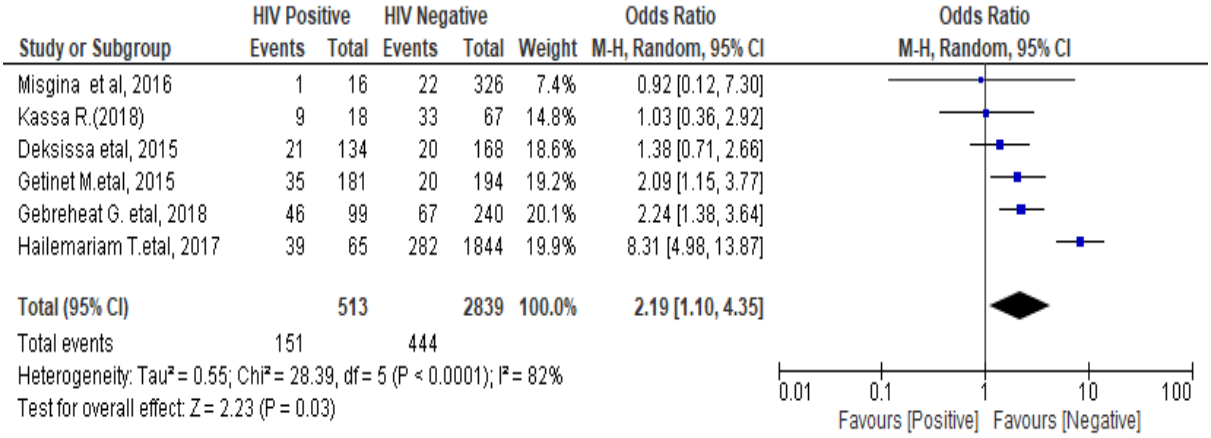

Figure 14: The association between HIV Status and precancerous cervical lesion among women in Ethiopia (n=6)

All studies(24, 46, 47, 50) except studies done in the Gurage zone (48) and Adama town (49), their 95% CIs cross the no effect line (null value). As result, the overall effect estimate (the diamond) also overlaps on the no effect line (Figure15).

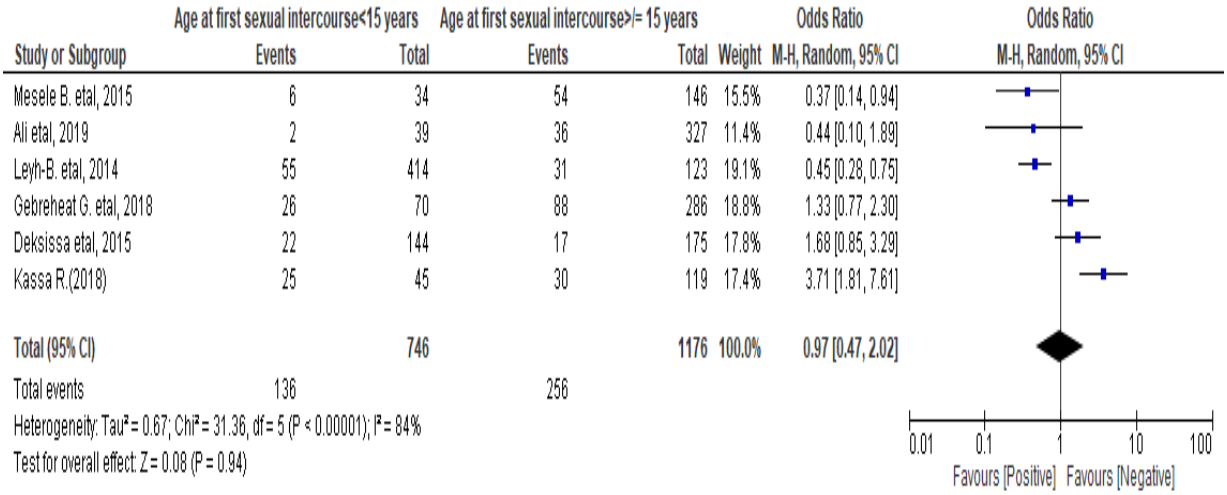

Figure 15: The association between age at first sexual intercourse and precancerous cervical lesion among women in Ethiopia (n=6)

This forest plot shows that the 95% confidence intervals of both studies(46, 47) overlap the line of no effect (null value). Consequently, the 95% confidence interval of the overall effect estimate overlaps the line of no effect (null value) (Figure 16).

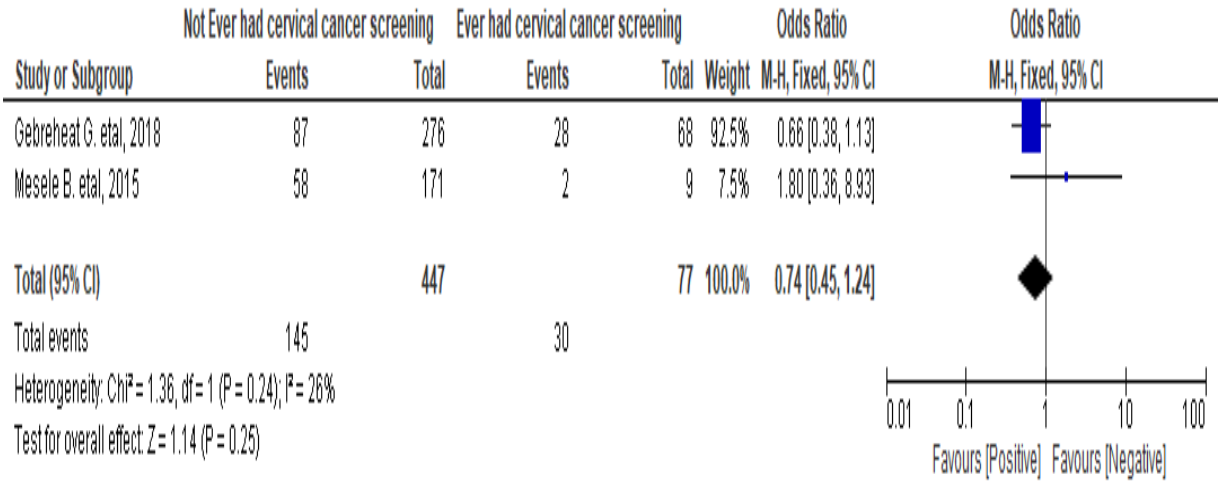

Figure 16: The association between ever had cervical cancer screening and precancerous cervical lesion among women in Ethiopia (n=2)

5. Discussion

Determining of the pooled prevalence estimate, the overall effect estimates for associated factors, assessment of heterogeneity between studies and the presence of publication bias were our central focus for this study

Therefore, the pooled prevalence estimate of precancerous cervical lesion among women in Ethiopia was (13.4%). The highest prevalence was observed in a study done in southern Ethiopia (16.5%)(21). Whereas the lowest point estimate was observed at a study conducted in northern Ethiopia in 2017(6.7%)(27). This pooled prevalence estimate of precancerous cervical lesion was comparable with the conducted in Egypt (10.4%)(16), china (15.54%)(13) and Latin America (16.1%)(11). But it was lower than the study conducted in Sudan (24%)(18) and the 5-year worldwide cervical cancer prevalence (9%) in 2012 (1). and higher than the study done in Qatari(8.1%)(14). These differences might be due to socio-economic variations.

At the meta-analysis level, each study was not given equal weights in the comparison. Those studies with wider 95% confidence intervals were given a lower weight than those studies having narrow confidence intervals or those studies with a larger square were had a higher weight and vice versa. As a rule of thumb, studies with a greater number of participants have narrow 95% confidence intervals and high precision to predict the pooled prevalence estimates. That means the bigger study has a smaller horizontal line (95% CI) and bigger square to predict the point prevalence estimate of precancerous cervical lesion and vice versa (Figure 4-16)

Statistically significant heterogeneity between studies was also detected (I^2=83.10% ($p<0.0001$). This might show that studies were inconsistent due to a reason other than chance (Table 4).

There was a variation of evidence reported on the effect of associated factors on precancerous cervical lesion like women's age, education, occupation, residence and age at first sexual intercourse. Some studies revealed that they had a statistically significant association with cervical cancer while others did not show a statistically significant association with cervical cancer at their study levels (Figure 6,8,9,10,16 & 17). This might be due to a difference in sample size, variance, methodology, study populations and reliability of the outcome measures at each study level.

At this meta-analysis level, the funnel plot indicated that there was possible publication bias upon discovering the prevalence of precancerous cervical lesion among women in Ethiopia (Figure 4).

The odd of precancerous cervical lesion were 68 % lower among married, widowed and divorced women than single women. It might be that all single women were not protected from the risk of cervical cancer infection (Figure 5).

There was no overall effect difference association with precancerous cervical lesion between non-formal educated and literate women (Figure7) as women residing Urban and rural (Figure 9), women ever had first sexual intercourse at < 15 years and ≥15 years (Figure 15) and women ever had cervical cancer screening and women did not ever have cervical cancer screening (Figure 16).

Being unemployed women did not have a clear difference effect on precancerous cervical lesion as compared to employed women (Figure 8).

Fewer episodes of precancerous cervical lesion were observed among women who did not have an experience of using modern contraceptives than users (Figure11). But more episode of cervical cancer was observed among women ever had >1-lifetime sexual partners than women ever had a 1-lifetime sexual partner (Figure 11)

The better outcome of precancerous cervical lesion was observed among women who did not have a history of STI than women having a history of STI (Figure 13).

Moreover, precancerous cervical lesion occurred less frequently among HIV negative women than HIV positive women (OR<1) (Figure 14).

6. Limitation of the study

This study was not conducted without limitations. Some of the limitations of this study are failure to show subgroup analysis due to a small number of studies were included and failure to show some important findings due presence of few important missing data at the study levels.

7. Conclusion and recommendations:

The pooled prevalence of cervical cancer among women in Ethiopia was high the 5-year worldwide cervical cancer prevalence (1). Some variables like income, being HIV positive, previous STI history, more than one number of lifetime sexual partners and prolonged uses of modern contraceptives were had a statistically significant association with the pooled prevalence estimates of cervical cancer among women in Ethiopia. There was also a variation of cervical cancer reports across studies in the country.

Therefore; reporting of this information in a consistent manner is important for researchers to enhance future studies and also useful for policymakers and practitioners for better understanding of the burden of cervical cancer in Ethiopia for prevention, diagnosis, and treatment of the disease.

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9. Annex

Annex 9. 1. JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies

Reviewer_____Date_____

Author _____Year_____Record Number----------

	Yes	No	Unclear	Not applicable
1. Were the criteria for inclusion in the sample clearly defined?	☐	☐	☐	☐
2. Were the study subjects and the setting described in detail?	☐	☐	☐	☐
3. Was the exposure measured in a valid and reliable way?	☐	☐	☐	☐
4. Were objective, standard criteria used for measurement of the condition?	☐	☐	☐	☐
5. Were confounding factors identified?	☐	☐	☐	☐
6. Were strategies to deal with confounding factors stated?	☐	☐	☐	☐
7. Were the outcomes measured in a valid and reliable way?	☐	☐	☐	☐
8. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Qureshi R, Mattis P, Lisy K, Mu P-F. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z (Editors). Joanna Briggs Institute Reviewer's Manual. The Joanna Briggs Institute, 2017. Available from https://reviewersmanual.joannabriggs.org/

Annex 9.2. JBI Critical Appraisal Checklist for Case Control Studies

Reviewer_____Date_____

Author _____Year_____Record Number_____

	Yes	No	Unclear	Not applicable
1. Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?	☐	☐	☐	☐
2. Were cases and controls matched appropriately?	☐	☐	☐	☐
3. Were the same criteria used for identification of cases and controls?	☐	☐	☐	☐
4. Was exposure measured in a standard, valid and reliable way?	☐	☐	☐	☐
5. Was exposure measured in the same way for cases and controls?	☐	☐	☐	☐
6. Were confounding factors identified?	☐	☐	☐	☐
7. Were strategies to deal with confounding factors stated?	☐	☐	☐	☐
8. Were outcomes assessed in a standard, valid and reliable way for cases and controls?	☐	☐	☐	☐
9. Was the exposure period of interest long enough to be meaningful?	☐	☐	☐	☐
10. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion) ----------

Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Qureshi R, Mattis P, Lisy K, Mu P-F. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z (Editors). Joanna Briggs Institute Reviewer's Manual. The Joanna Briggs Institute, 2017. Available from https://reviewersmanual.joannabriggs.org/

Annex 9.3. JBI Critical Appraisal Checklist for Cohort Studies

Reviewer_____Date_____
Author _____Year_____Record Number _____

	Yes	No	Unclear	Not applicable
1) Were the two groups similar and recruited from the same population?	☐	☐	☐	☐
2) Were the exposures measured similarly to assign people	☐	☐	☐	☐
3) to both exposed and unexposed groups?				
4) Was the exposure measured in a valid and reliable way?	☐	☐	☐	☐
5) Were confounding factors identified?	☐	☐	☐	☐
6) Were strategies to deal with confounding factors stated?	☐	☐	☐	☐
7) Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	☐	☐	☐	☐
8) Were the outcomes measured in a valid and reliable way?	☐	☐	☐	☐
9) Was the follow up time reported and sufficient to be long enough for outcomes to occur?	☐	☐	☐	☐
10) Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	☐	☐	☐	☐
11) Were strategies to address incomplete follow up utilized?	☐	☐	☐	☐
12) Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include☐ Exclude ☐ Seek further info☐

Comments (Including reason for exclusion) ----------

Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Qureshi R, Mattis P, Lisy K, Mu P-F. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z (Editors). Joanna Briggs Institute Reviewer's Manual. The Joanna Briggs Institute, 2017. Available from https://reviewersmanual.joannabriggs.org/

Annex 9.4. JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data

Reviewer_____Date_____

Author _____Year_____Record Number _____

	Yes	No	Unclear	Not applicable
1. Was the sample frame appropriate to address the target population?	☐	☐	☐	☐
2. Were study participants sampled in an appropriate way?	☐	☐	☐	☐
3. Was the sample size adequate?	☐	☐	☐	☐
4. Were the study subjects and the setting described in detail?	☐	☐	☐	☐
5. Was the data analysis conducted with sufficient coverage of the identified sample?	☐	☐	☐	☐
6. Were valid methods used for the identification of the condition?	☐	☐	☐	☐
7. Was the condition measured in a standard, reliable way for all participants?	☐	☐	☐	☐
8. Was there appropriate statistical analysis?	☐	☐	☐	☐
9. Was the response rate adequate, and if not, was the low response rate managed appropriately?	☐	☐	☐	☐

Overall appraisal: Include☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion) ----------

Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and incidence data. Int J Evid Based Healthc. 2015;13(3):147–153.

Annex9.5. JBI Critical Appraisal Checklist for Systematic Reviews and Research Syntheses

Reviewer_____Date_____

Author _____Year_____Record Number

	Yes	No	Unclear	Not applicable
1. Is the review question clearly and explicitly stated?	☐	☐	☐	☐
2. Were the inclusion criteria appropriate for the review question?	☐	☐	☐	☐
3. Was the search strategy appropriate?	☐	☐	☐	☐
4. Were the sources and resources used to search for studies adequate?	☐	☐	☐	☐
5. Were the criteria for appraising studies appropriate?	☐	☐	☐	☐
6. Was critical appraisal conducted by two or more reviewers independently?	☐	☐	☐	☐
7. Were there methods to minimize errors in data extraction?	☐	☐	☐	☐
8. Were the methods used to combine studies appropriate?	☐	☐	☐	☐
9. Was the likelihood of publication bias assessed?	☐	☐	☐	☐
10. Were recommendations for policy and/or practice supported by the reported data?	☐	☐	☐	☐
11. Were the specific directives for new research appropriate?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)----------

Aromataris E, Fernandez R, Godfrey C, Holly C, Kahlil H, Tungpunkom P. Summarizing systematic reviews: methodological development, conduct and reporting of an Umbrella review approach. Int J Evid Based Healthc. 2015; 13(3):132-40.