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Exploring the role of cervicovaginal microbiota as risk factor for cervical cancer in Sub-Saharan Africa: a systematic review and meta-analysis

By

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Abstract

Objective To estimate the association between cervico-vaginal microbiota and cervical cancer in Sub-Saharan Africa.

Study design Systematic Review and Meta-Analysis.

Method The databases, PubMed and African Journal Online (AJOL), as well as Google Scholar, were accessed. All primary studies (cross-sectional, cohort and case control) that reported cervical cancer, risk factors and cervico-vaginal microbiota in Sub-Saharan Africa, which were written in English language, were screened. Methodological and quality assessment of included studies was carried out using Joanna Briggs Institute (JBI) quality assessment tool. Random effects model meta-analysis was performed using MedCalc statistical software version 20.0.1 to evaluate the pooled prevalence of cervico-vaginal microbiota and prevalence was determined using the Freeman-Tukey double arcsine transformation. Heterogeneity between studies was assessed using the I-squared (I^2) test and publication bias evaluated using Egger's statistical test. The study protocol was registered with the PROSPERO database (No: CRD42024495232).

Results The review involved screening of a total of 1,151 articles and 15 articles, which met the inclusion criteria, were finally used for the review and meta-analysis. Cervico-vaginal risk factors noted in our study comprised infection with high risk human papilloma virus (hrHPV), human Immune virus (HIV), *Trichomonas vaginalis*, *Porphyromonas*, *Prevotella*, and *Anaeromonas*. The pooled prevalence of HPV in the included studies was 40% (95% Confidence interval [CI]– 24%, 56%) and pooled prevalence of HIV as a risk factor was 19% (95% CI- 3%, 44%). For each individual meta-analysis, high heterogeneity was observed with I^2 of 98.97 (HPV) and 99.33 (HIV) at p-values ≤ 0.01. Egger's tests for regression intercept in funnel plots indicated no evidence of publication bias while JBI result showed high quality of included articles.

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Conclusion This systematic review and meta-analysis revealed that cervico-vaginal microbiota, such as *Porphyromonas*, *Prevotella*, and *Trichomonas vaginalis*, along with high-risk HPV and HIV infection, increase cervical cancer risk in Sub-Saharan Africa. To reduce this burden, integrating microbiota management, sexual health education and HPV vaccination, is crucial.

Keywords Cervical cancer, Cervico-vaginal microbiota, HPV, sub-Saharan Africa

Introduction

Worldwide, cervical cancer is the fourth most diagnosed cancer in women and fourth highest cause of cancer death (next to breast, colorectal and lung cancers) [1]. In 2020, an estimate of 604,000 new cases and 342,000 deaths was reported. It is estimated that 1 in 70 women worldwide will develop cervical cancer before reaching 79 years of age [2, 3]. Africa is disproportionately affected, with sub-Saharan Africa accounting for the highest incidence and mortality from cervical cancer [1]. The cause of most cancer deaths, which was put at 85%, in 46 out of 54 Sub-Saharan African countries was attributed to cervical cancer and this has continued to rise [3]. Human Papilloma Virus(HPV), the established causative agent for cervical cancer has been implicated in about 4.8% of all cancers. This percentage drastically increases in less developed regions of the world, with HPV attributed to 14.2% of all cancers in sub-Saharan Africa [1]. The HPV has been implicated in the aetiology of cervical cancer [3, 4]. However there are other risk factors that potentiate the progression of HPV infection to cervical cancer. Other cofactors such as, sexually transmitted infections,*Chlamydia trachomatis*, HIV, Pelvic Inflammatory disease [PID], multiparity, early coitarche, multiple sexual partners, long term use of oral contraceptives, low socioeconomic status, poor availability and unaffordability of screening and treatment modalities, and cervico-vaginal microbiota composition have been shown to potentiate progression of HPV infection to cervical cancer [5, 6]. These factors are more in developing nations such as sub-Saharan Africa than developed nations.

Most cervico-vaginal microbiota such as *Chlamydia*, *Gonorrhea*, and *Mycoplasma hominis*, have been isolated in cervical cancer cases, and have been noted to be significantly different from microbiota isolated from precancerous lesions and healthy women [7, 8]. More so, other studies have noted the presence of *Fusobacterium* spp., *Campylobacter* spp., *Peptostreptococcus* spp., *Haemophilus* spp. and highly reduced *Lactobacilli* spp. in cervical cancer cases, which was different from the microbial pattern in healthy women [9]. This therefore suggests a strong correlation between cervico-vaginal microbiota and cervical cancer risk and progression [7, 10]. These cervico-vaginal microbiota among healthy women and cervical cancer patients have also been shown to vary among different races and ethnic groups [11, 12]. To ensure early diagnosis, treatment and ultimately eliminate cervical cancer in this region, knowledge and identification of predisposing factors such as cervico-vaginal microbiota is necessary. Therefore, this meta- analysis was aimed at identifying cervico-vaginal microbiota among cervical cancer patients in sub-Saharan Africa. This would bridge the knowledge gap and help clinicians determine the antibiotics to use on these patients especially in low resource settings like sub-Saharan Africa.

Materials and methods

Study design PROSPERO which is an international prospective registration for systematic reviews was searched for to ensure that identical review had not been conducted. The protocol for this review was designed and registered on PROSPERO with the registration number CRD42024495232 after search did not identify identical review.

Search strategy

Various electronic search engines such as PubMed, Google Scholar and African Journal Online were used to search for studies from December 7 to 24, 2023. The search was re-run from July 7 to 15, 2024. Search was conducted through the combination of various key words including 'Risk factors, microbiota, microorganisms, cervical cancer, different countries in sub-Saharan Africa and Sub-Saharan Africa' by using Boolean operators in the different databases. Furthermore, references from various articles sourced were checked to identify relevant studies for possible addition.

Eligibility criteria

Inclusion criteria These comprised;

1. Studies that focused on microorganisms as part of the risk factors for cervical cancer.
2. Studies that involved cervical cancer and other types of cancer.
3. Studies that focused only on women in Sub-Saharan Africa.
4. Cross-sectional, cohort, and case-control studies.

Exclusion criteria These comprised;

1. Studies that focused only on other cancers outside cervical cancer.

2. Studies that did not involve microorganisms as risk factors for cervical cancer.
3. Studies not conducted in Sub-Saharan Africa.
4. Retrospective studies.

Appraisal and study selection

Zotero application, a referencing manager was used to remove duplicate articles. Two independent reviewers, MIA and CKE, reviewed the title and abstract of identified articles. After that, full text review was done and in case of any discrepancy, the third reviewer LOA (adjudicator) helped to resolve the discrepancy. The studies were subjected to quality assessment, which was done also by MIA and CKE, using Joana and Briggs appraisal tool for cross-sectional, cohort, and case-control studies. The critical appraisal criteria used in rating the included studies, an eight-question scale was answered for cross sectional studies, nine question scale for case-control studies and ten question scale for cohort studies. The questions were answered by "yes, no, and not clear" with each making a point. If the number of "yes" was more than six (6), the article was of high quality, 4–5 was standard quality and 3 and below was low quality. The table of quality assessment is shown below in Table 1.

Data extraction

Data extraction was done using a structured extraction table, by two independent authors, MIA and CKE. Relevant data collected comprised author name, study year, country, study design, participants, sample size, risk factors, number of positive microbial risk factors, and screening method for cancer detection and microbial detection.

Statistical analysis

MedCalc statistical software version 20.0.1 was used to perform meta-analyses. The pooled prevalence was evaluated using proportion command based on random effects model due to possibility of heterogeneity (sample size) among the included studies while prevalence was determined using the Freeman-Tukey double arcsine transformation. Due to the high possibility of heterogeneity among the studies, heterogeneity was assessed using the I [2] test, with the values 25%, 50%, and 75% suggesting low, intermediate, and high heterogeneity respectively within the study [13]. Systematic reviews and meta-analysis could be skewed due to the tendency of adding high-quality and statistically significant studies which pointed in a preferred direction; hence, publication bias was evaluated using Egger's test [14].

A total of 1,151 results were retrieved from two databases comprising 627 and 333 from PubMed and AJOL respectively, and 191 from Google Scholar. Screening of titles and abstracts reduced the articles to 67 after removal of 1,084 articles (duplicates, studies not in sub-Saharan Africa, studies not on cervical cancer, review articles, and other irrelevant articles). A full text assessment of 67 articles was done and 52 were further excluded after not meeting the inclusion criteria. Finally, 15 articles were included for the systematic review and meta-analysis. The studies were reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) protocol (Fig. 1) [15].

Characteristics of included studies

The included studies comprised twelve cross sectional studies,[5,16–20,22–25,27,28] two case-control studies [21, 26],

Table 1 Table of quality assessment

Author	1	2	3	4	5	6	7	8	9	10
Cross sectional										
Haile et al., 2019	yes	yes	no	yes	yes	yes	Yes	yes		
Kennedy et al., 2015	yes	no	no	yes	yes	yes	Yes	yes		
Magaji et al., 2024	yes	yes	-	yes	yes	yes	Yes	Yes		
Tesfaye et al., 2024	yes	no	Yes	Yes	Yes	Yes	Yes	Yes		
Anastos et al., 2005	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		
Lazenby et al., 2014	Yes	Yes	Yes	Yes	No	No	Yes	Yes		
Ali et al., 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		
Musa et al., 2023	Yes	Yes	No	No	No	Yes	Yes	Yes		
Catarino et al., 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		
Sebastien, 2023	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes		
Taku et al., 2023	Yes	Yes	No	Yes	Not Clear	Not Clear	Yes	Yes		
Case control										
Adjorlolo-Johnson et al., 2010	Yes	No	Yes	Yes	Yes	No	No	Yes	No	Yes
Holmes et al., 2009	Yes	No	No	Yes	Yes	No	Yes	Yes	No	Yes
Teka et al., 2023	No	No	Yes	Yes	Yes	Not Clear	Not Clear	Yes	Yes	Yes
Cohort										
Luckett et al., 2022	Yes	Yes	Yes	No	No	Yes	Yes	Yes	-	Yes

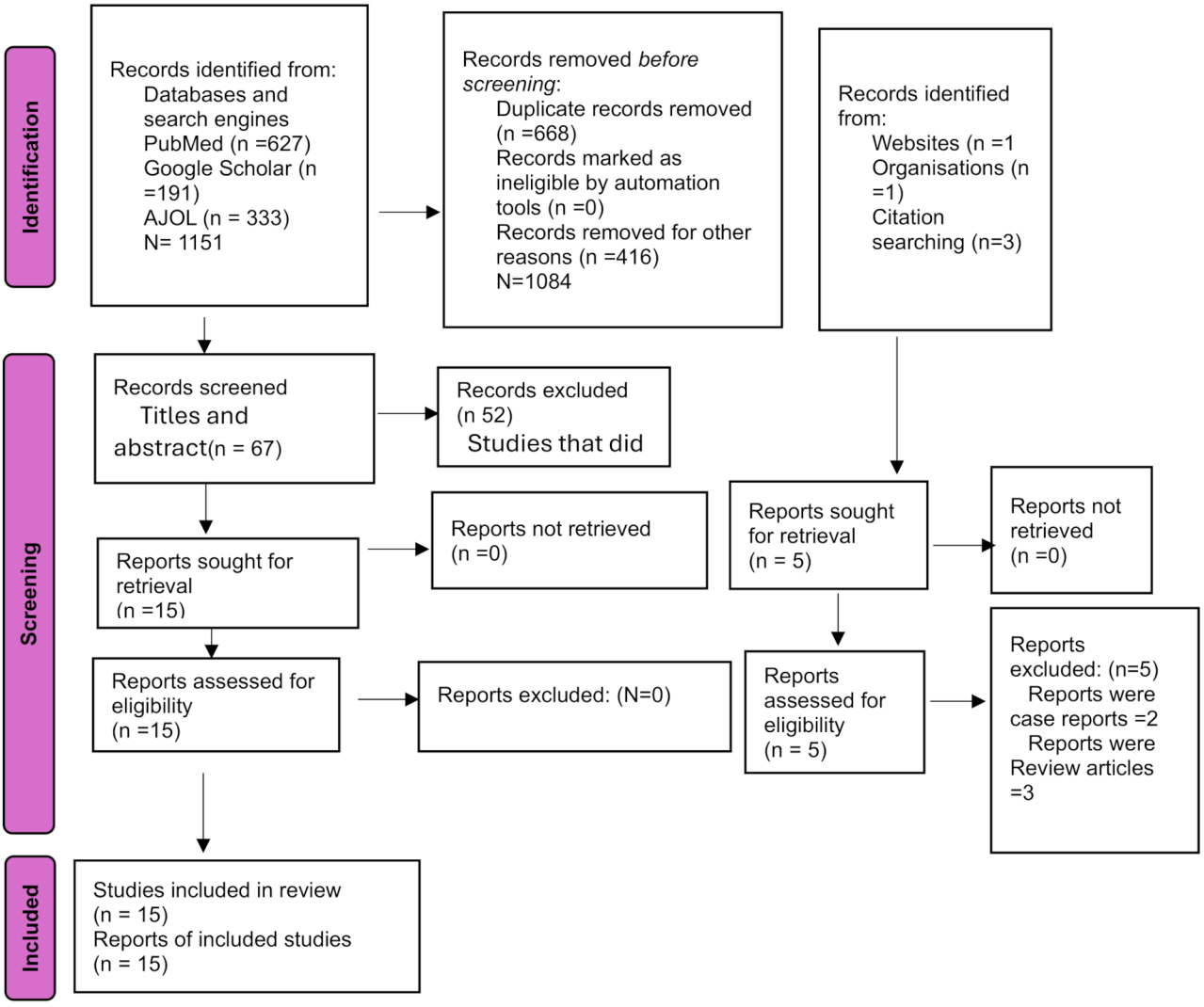

Fig. 1 PRISMA flow chart

and one cohort study [29]. A total of four studies combined both the microbial risks factors and lifestyle risk factors [16–19]. All the included studies were done in sub-Saharan Africa, comprising four studies in Ethiopia [16, 20, 23, 28], three studies in Nigeria [17, 18, 24], two studies in Tanzania [5, 27], and one study each in Cote d'Ivoire [21], Senegal [26], Rwanda [19], Botswana [29], Cameroon [22], and Namibia [25]. Screening methods for cervical cancer was Pap smear cytology while polymerase chain reaction (PCR) was used for microbial deoxyribonucleic acid (DNA) detection. All cervical cancer cases were histologically confirmed. Results of quality assessment showed that all the studies were of good quality based on the score range of 5 to 8 (Table 2).

Results

Risk factors associated with cervical cancer

Microbiota as risk factors

Out of the 15 studies that reported microbiota as risk factors associated with cervical cancer, 13 studies reported HPV as a risk factor for cervical cancer. The pooled prevalence of HPV in the included studies was 40% (95% Confidence interval [CI] 24%, 56%) (Fig. 2). Some studies reported different genotypes of HPV that were implicated with cervical cancer. The common genotypes reported comprised HPV 16, 18, 31, and 35 [17, 20, 21]. Four studies reported that both HPV and Human immunodeficiency virus (HIV) were risk factors for cervical cancer [5, 16, 21, 22]. Also, six studies reported that HIV was a risk factor and the pooled prevalence of HIV as a risk factor was 19% (CI 3%, 44%) (Fig. 3).Three studies reported bacterial species as risk factors and these species comprised *Bacteroides* spp., *Trichomonas vaginalis*,

Table 2 Characteristics of included studies

Author	Year	Country	Study design	Sample size	Risk factors		Screening method	Q.A (JB)
					Microbiota/No.	Life style		
Haile	2019	Ethiopia	Cross sectional	66	HPV (15) HIV (4)	Smoking Contraceptives	RIATOL qPCR HPV genotyping	7
Kennedy	2015	Nigeria	Cross sectional	80	HPV (8)	Sexual partners, smoking, history of STDs, early sex debut	PCR	6
Adjorlolo-Johnson	2010	Cote d'Ivoire	Case control	132	HPV (118) HIV (22)		Pap smear test PCR	6
Magaji	2024	Nigeria	Cross sectional	957	HIV (570)	Smoking Contraceptives STDs	Pap smear test	7
Holmes	2009	Senegal	Case control	150	HIV (10)			6
Tesfaye	2024	Ethiopia	Cross sectional	247	HPV (24)		Pap smear rest PCR	7
Anastos	2005	Rwanda	Cross sectional	710	HPV (476)	Contraceptive multiple sexual partners	PCR	7
Lazenby	2014	Tanzania	Cross sectional	323	HPV (42) *T. vaginalis*		liquid-basedcytology	6
Luckett	2022	Botswania	Cohort	300	HPV (88)		liquid-basedcytology	8
Ali	2019	Ethiopia	Cross sectional	366	HPV (50)		Pap smear test PCR	8
Musa	2023	Nigeria	Cross sectional	138	HPV (68)		real-time (qPCR)	6
Catarino	2016	Cameroon	Cross sectional	838	HPV (285) HIV (64)		PCR	8
Sebastien	2023	Namibia	Cross sectional	49	HPV (8)			5
Teka	2023	Ethiopia	Cross sectional	120	HPV (93) *Porphyromonas*, *Provotella*, *bacteroides*, *Anaerococcus spp*.		PCR	6
Klein	2019	Tanzania	Cross-Sectional	134	HPV (126), HIV (39), *Bacteroides*, *Fusobacteria*		PCR	6

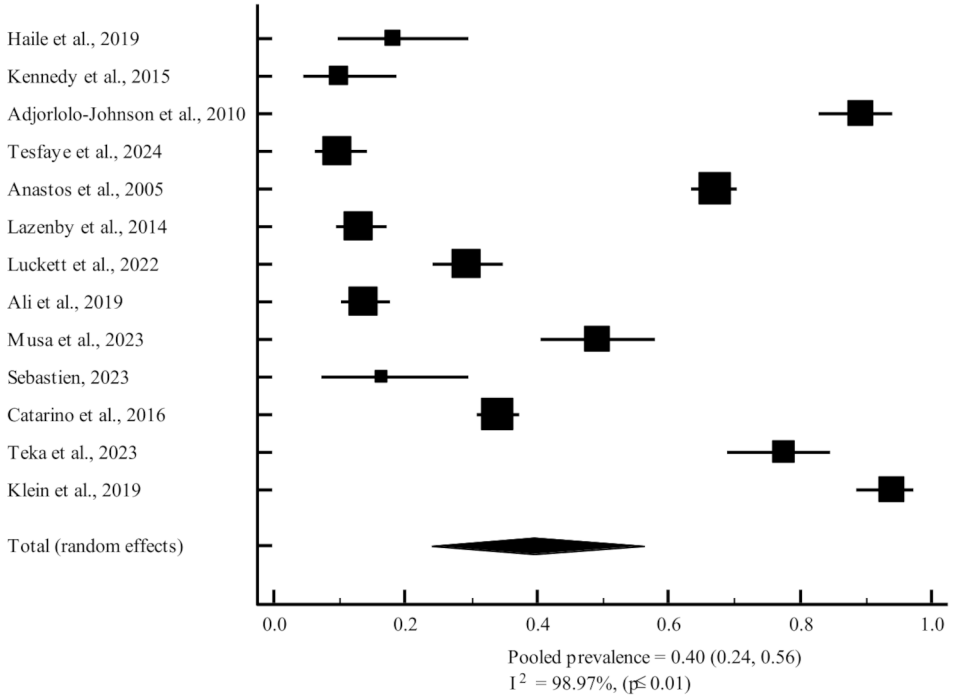

Fig. 2 Pooled prevalence of HPV among the cervical cancer patients

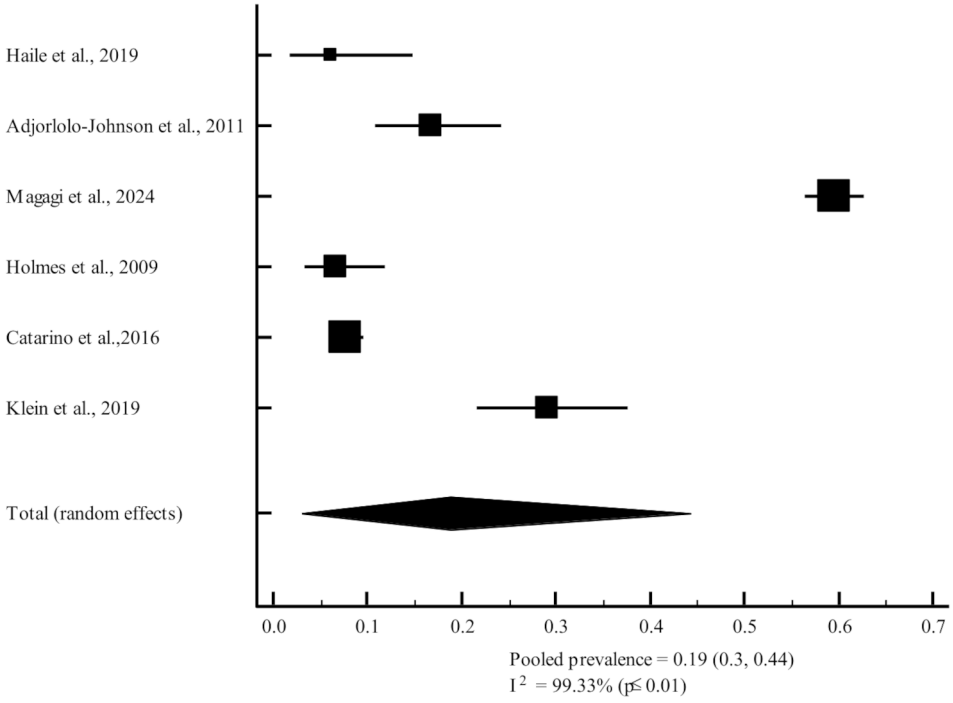

Fig. 3 Pooled prevalence of HIV among the cervical cancer patients

Porphyromonas, *Prevotella*, *Anaeromonas* and *Fusobacteria* [5, 23, 24].

Screening methods for cervical cancer

There were two screening methods adopted in the eligible studies and they were: cervical smear cytology screening and DNA screening of microbial risk factors. Papanicolaou smear cytology screening was the predominant cervical cancer screening method used in the studies [18, 20, 21, 25]. This was followed by liquid-based cytology [25, 26]. Polymerase chain reaction(PCR) was used for DNA screening of microbial agents associated with cervical cancer.[5,16–17,19–23,28]

Assessment of heterogeneity and publication bias

Two meta-analyses were carried out and the results showed high heterogeneity. The I^2 of the pooled prevalence of HPV and HIV were 98.97% and 99.33% respectively. Different sample sizes resulted in high heterogeneity. Egger's test for a regression intercept gave a *p*-value of 0.9666 (HPV) and 0.5091 (HIV) indicating no evidence of publication bias [14]. Also, funnel plots results showed that most studies used large sample sizes which affected their precision (Figs. 4 and 5).

Discussion

This study showed that the cervico-vaginal risk factors for cervical cancer in sub-Saharan Africa comprised hrHPV, HIV, *Trichomonas vaginalis*, *Porphyromonas*, *Prevotella*, and *Anaeromonas*. The pooled prevalence of HPV and HIV in the included studies were 40% (95% Confidence interval [CI]– 24%, 56%) and 19% (95% CI-3%, 44%) respectively.

Cervico-vaginal microbial population of healthy women is mostly dominated by lactobacillus. In a study, regardless of the presence of cervical cancer or dysplasia, alpha and beta diversity was compared between women who were HPV-positive and those who were HPV-negative. It was found that there were notable differences in beta diversity between the two groups of women, but not in alpha diversity analysis [23]. The group's observed microbial diversity raises the possibility that the composition and variety of the microbiota may differ depending on the cervical cancer diagnosis. Additionally, women with cervical cancer had higher genera and specie diversity than healthy women [23]. These findings imply that carcinogenesis destroys the stable composition of cervico-vaginal flora, which is primarily *Lactobacillus spp*. supplemented by other bacteria, leading to an increase in microbial diversity. Similar investigations have also confirmed this finding [11]. The microbial diversity among cervical cancer patients in sub-Saharan Africa may also be due to injudicious use of antibiotics before their presentation at the hospitals. The injudicious use of antibiotics among these women leads to destruction of the normal cervico-vaginal flora and reduction in host immunity thereby increasing the risk of microbial diversity [30].

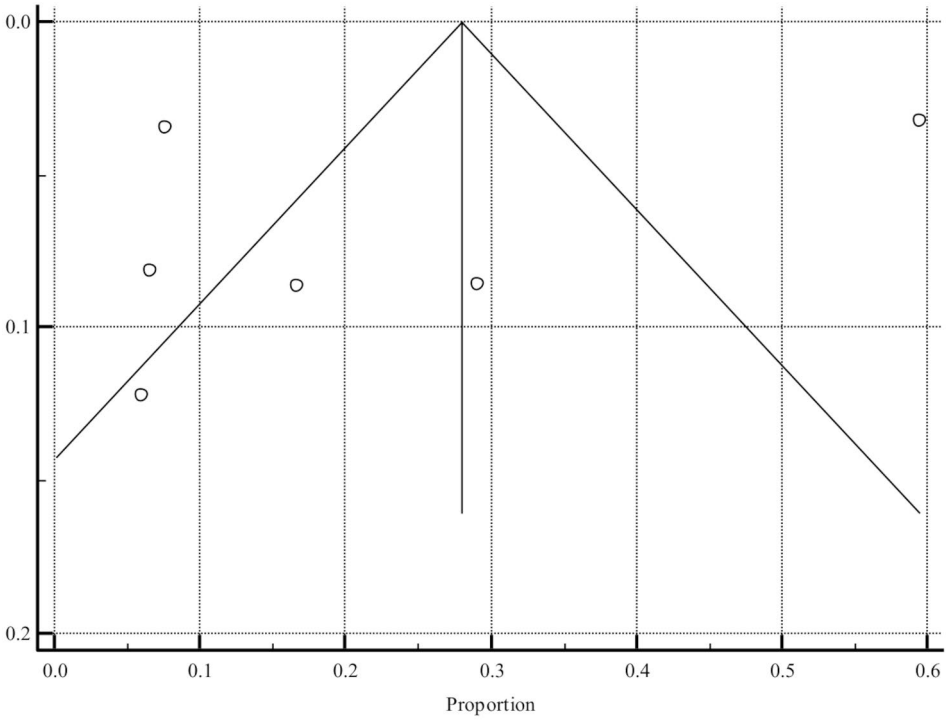

Fig. 4 Funnel plot for HPV prevalence among the cervical cancer patients

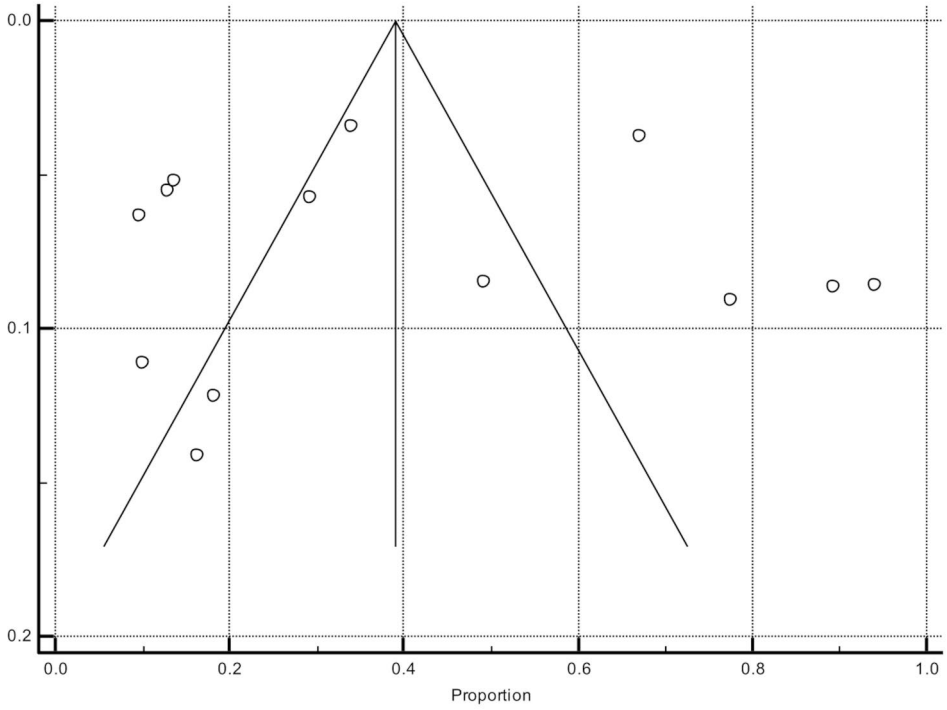

Fig. 5 Funnel plot for HIV prevalence among the cervical cancer patients

The pooled prevalence of high risk HPV at 40% in this study was higher than the global prevalence at 21% [31]. It was also higher than 34% previously reported in sub-Saharan Africa [32]. A previous study had reported that cervico-vaginal microbes play a specific role in HPV persistence and cervical cancer development and progression [28]. HPV has been documented as an aetiologic agent of cervical cancer. Previous studies reported that different genotypes of HPV were implicated with cervical cancer. The common genotypes in the included studies comprised HPV 16, 18, 31, and 35. HPVs 16 and 18 were the most commonly implicated strains that cause cervical cancer and both strains accounted for about 70% of cases of cervical cancer [33, 34]. Using specimens from Ghana, South Africa, and Nigeria, 90.4% of invasive cervical cancers were HPV positive [35].

The 19% pooled prevalence of HIV among cervical cancer patients in sub-Saharan Africa could be attributed to HIV pandemic in this region. In a study by Klein et al., HIV was shown to have a significant effect on the cervico-vaginal microbiome by increasing bacterial richness but decreasing its beta diversity [5]. These results are similar to what has been reported for the cervico-vaginal microbiota and suggest that changes in the cervical epithelium microenvironment brought on by HIV exert some selective pressure on cervical bacterial communities [36, 37]. Despite rising antiretroviral treatment (ART) coverage, cervical cancer is predicted to become a more serious issue as the global HIV-positive population rises. Cervical cancer risk is not significantly affected by ART, and recurrent rates remain high with or without treatment, in contrast to the risk reduction shown after ART in other AIDS-defining malignancies such as Kaposi's sarcoma and non-Hodgkin's lymphoma [38, 39].

Three studies reported bacterial species as risk factors and these species comprised *Bacteroides spp*, *Trichomonas vaginalis*, *Porphyromonas spp*, *Prevotella spp*, *Anaeromonas spp* and *Fusobacteria spp* [5, 23, 24]. The findings in this review were essentially similar to those of other studies done outside sub-Saharan Africa [10, 40, 41]. Wu et al., identified *Porphyromonas* and *Prevotella* as cervical cancer marker genera [42]. The role of *Porphyromonas* and *Prevotella* in carcinogenesis has also been reported in oral cancer [43]. This involves three different possible modes of action: production of carcinogenic compounds, anti-apoptotic activity, and chronic inflammation [43]. These bacteria generate inflammatory mediators that promote angiogenesis, mutagenesis, oncogene activation, and cell proliferation. Oral cavities are home to *Porphyromonas gingivalis*, which has been shown to produce lipopolysaccharides that stimulate the production of proinflammatory cytokines by CD4 + T helper cells and macrophages, including tumor necrosis factor (TNF-) and interleukin-1(IL-1) [42]. Additionally, research has shown that *Porphyromonas gingivalis* can mediate many signaling pathways that affect inflammation, anti-apoptosis, cell invasion, and the cell cycle.[44] It may be possible to use specific cervico-vaginal microbiota as diagnostic

markers for people who are highly likely to develop cervical cancer. Additionally, probiotics or antibiotics may be developed as preventive measures to treat genital infections caused by bacteria that potentiate cervical cancer. Bacterial colonization with a microbiota linked to healthy cervical cytology should be encouraged.

Longitudinal investigations of the cervico-vaginal microbiota are necessary to comprehend the temporal evolution of microbial populations, especially in patients with high-grade squamous intraepithelial lesions (HSIL). Long-term longitudinal research will make it possible to identify early modifications in the cervico-vaginal microbiota that could be useful in predicting the emergence of precancerous lesions. Such research would need to be huge because the process of HPV infection leading to cervical cancer takes decades, and in many cases, the disease never develops at all. Metagenomic sequencing, as opposed to 16 S or other shallow targeted sequencing methods, can further improve studies of the cervico-vaginal microbiome.

Strengths and limitations

This study is the first systematic review and meta-analysis specifically assessing the cervico-vaginal microbiota and its association with cervical cancer risk in sub-Saharan Africa. This study used robust statistical methods, including random-effects modeling and the Freeman-Tukey double arcsine transformation, to account for variability across studies. The quality of included studies was rigorously assessed using the Joanna Briggs Institute tool, ensuring that only high-quality studies were included and analyzed. However, the limitations of this study comprise the high heterogeneity ($I^2 > 98\%$) observed across the included studies thereby indicating variability in study design, population, and methodology. Secondly, only English-language articles were included, which may have limited the generalizability of findings to non-English speaking regions of Sub-Saharan Africa. The limited number of included studies ($n = 15$) may not comprehensively represent the cervico-vaginal microbiota landscape across all sub-Saharan African countries.

Conclusion

This systematic review and meta-analysis provided evidence that cervico-vaginal microbiota, particularly the presence of high risk HPV, HIV,*Trichomonas vaginalis*, *Porphyromonas*, *Prevotella*, and *Anaeromonas*. were significantly associated with increased cervical cancer risk in sub-Saharan Africa.

Recommendations

These findings therefore underscore the need for integrating microbiota management, sexual health education, and targeted preventive interventions, such as HPV vaccination, to reduce the burden of cervical cancer in the region. Further research is required to explore the potential for therapeutic modulation of the microbiota as a cancer preventive strategy.

Abbreviations

CD4	Cluster of Differentiation 4
GLOBOCAN	Global Cancer Incidence, Mortality And Prevalence in Oncology
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
HSIL	High-grade Intraepithelial Lesion
IARC	International Agency for Research on Cancer
IL	Interleukin
PID	Pelvic Inflammatory Disease
STD	Sexually Transmitted Disease
TNF	Tumour necrosis factor

Author contributions

MIA was involved in the concept, design, planning, conduct, data analysis, and manuscript writing of this research project. MEUD was involved in the concept, design, planning, conduct, data analysis, and manuscript writing of this research project. LOA was involved in the concept, design, planning, conduct, data analysis, and manuscript writing of this research project. VNC was involved in the design, planning, conduct, data analysis, and manuscript writing of this research project. CKE was involved in the conduct, data analysis, and manuscript writing of this research project. GUE was involved in the conduct, data analysis, and manuscript writing of this research project. FOI was involved in the conduct, data analysis, and manuscript writing of this research project.

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Data availability

All datasets generated and analysed, including the study protocol, search strategy, list of included and excluded studies, data extracted, analysis plans, and quality assessment, are available in the article and upon request from the corresponding author.

Declarations

Ethics approval and consent to participate

Ethical approval was not required for this systematic review as the research was based on information retrieved from published studies.

Consent for publication

The consent to publish this manuscript was obtained from all the authors.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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