PREVALENCE, CHARACTERISTICS AND TREATMENT OUTCOMES OF HPV POSITIVE OROPHARYNGEAL CARCINOMA IN AFRICA: A SYSTEMATIC REVIEW AND META-ANALYaSIS.

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ABSTRACT

Background: **Human papillomavirus (HPV) is a sexually transmitted virus implicated in several anogenital and oropharyngeal malignancies. Rising oral sexual practices have been suggested as one factor influencing oral HPV transmission and associated malignancies in some populations. This review aimed to estimate the pooled prevalence, summarize characteristics, and synthesize treatment and outcome data for HPV-positive oropharyngeal carcinoma (OPC) in Africa.**

Methods: **An initial PROSPERO registration was done (CRD420251012776), and the systematic review followed the PRISMA guidelines. The study included original English peer-reviewed research works that reported data on the prevalence, characteristics, and treatment outcomes of HPV-positive oropharyngeal cancers. The risk of bias was assessed for all the studies using Cochrane's ROBIN-E tool. Systematic synthesis and meta-analysis were used to synthesise extracted data.**

Results: **15 studies involving a total of 896 participants met the inclusion criteria and were included in the meta-analysis. The pooled prevalence of HPV-associated oropharyngeal cancer across the 15 African-based studies was 12% (95% CI: 8%–19%), with significant heterogeneity (I^2 = 70.2%). The test for subgroup differences was statistically significant (Chi^2 = 10.94, p = 0.012), indicating that detection methods may influence reported prevalence rates. Treatment and outcome data were sparsely reported; only one study provided detailed follow-up outcomes.**

Conclusion: **There were limited data of treatment and outcomes underscoring the need for improved reporting standards and longitudinal data across African settings.**

Keywords: Human papilloma virus, HPV Prevalence, Oral HPV, Oropharyngeal carcinoma, Africa

INTRODUCTION

Human papillomavirus (HPV)–associated oropharyngeal carcinoma (OPC) has emerged as a distinct and increasingly prevalent subset of head and neck cancers globally.[1-3] While the overall incidence of tobacco- and alcohol-related OPC has declined in many regions, HPV-driven OPC continues to rise, particularly in high-income countries.[2,3] This epidemiological shift has been attributed to changes in sexual behaviours, including increased oral sexual practices, as well as improved diagnostic recognition of HPV-related disease. However, in Africa, the epidemiology of HPV-associated OPC remains less clearly defined due to limited data, variability in diagnostic capacity, and differences in underlying risk factors such as HIV prevalence and healthcare access.[1,2]

Human papillomavirus is a small, non-enveloped double-stranded DNA (DeoxyNucleic Acid) virus that belongs to the Papillomaviridae family.[1] It is broadly classified into high-risk and low-risk types based on oncogenic potential. High-risk types, particularly HPV-16 and HPV-18, are strongly implicated in the pathogenesis of OPC, with HPV-16 accounting for the majority of HPV-positive cases.[2, 3] Other high-risk types, including HPV-31, 33, 35, and 45, have also been identified, though their relative contribution is less

pronounced.[2] In contrast, low-risk types such as HPV-6 and HPV-11 are typically associated with benign lesions.[1,2]

Oropharyngeal carcinomas, a subset of head and neck cancers, represent a significant global health burden and are collectively the seventh most commonly diagnosed malignancy worldwide.[4] The global prevalence of OPC is estimated at approximately 1.1 per 100,000, contributing to the broader burden of 758,000 cases of cancers of the lip, oral cavity, and pharynx annually.[5,6] Major risk factors include tobacco use, alcohol consumption, and HPV infection, with regional variation influenced by differences in sexual behaviours, HIV prevalence, and diagnostic capacity, particularly across Africa.[1,2] Evidence from Sub-Saharan Africa indicates that HPV-related OPC remains under-characterized; for instance, a systematic review by Okerosi et al. reported p16 positivity rates of 13.6% overall and 20.3% specifically among oropharyngeal cancers, with p16 immunohistochemistry and HPV polymerase chain reaction being the most commonly used diagnostic methods.[4] However, the absence of pooled prevalence estimates and the heterogeneity of diagnostic approaches limit the comparability and generalizability of these findings across the continent.

Despite growing global evidence, data from Africa remain sparse, geographically uneven, and methodologically heterogeneous. Existing studies are concentrated in a limited number of countries and employ varying diagnostic approaches, including p16 immunohistochemistry and HPV DNA detection via polymerase chain reaction, which complicates cross-study comparisons.[1,4,6] Furthermore, there is a lack of robust pooled prevalence estimates and limited reporting of treatment modalities and clinical outcomes across the continent.

Therefore, this study aimed to assess the prevalence, explore the characteristics including epidemiological distribution, diagnostic methods and treatment patterns, and assess the treatment outcome data for HPV-positive oropharyngeal carcinoma in Africa by synthesizing existing original studies.

METHODS

Study reporting and registration

This review was conducted and reported per the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline.[7] The study protocol was registered with PROSPERO (International Prospective Register of Systematic Reviews) with registration number CRD420251012776, where a detailed methodological framework was outlined.

This review was guided by the following research question:

1. What is the pooled prevalence of HPV-positive oropharyngeal carcinoma in Africa?
2. What are the associated characteristics (epidemiological patterns, diagnostic approaches and treatment modalities) of HPV-positive oropharyngeal carcinoma in Africa?
3. What are the treatment outcomes of HPV-positive oropharyngeal carcinoma in Africa*?*

Search strategy

A systematic search of available literature was conducted across electronic databases to identify all studies on the study theme **(Figure 1).** The search retrieved studies from PubMed, Google Scholar, Science Direct, DOAJ (Directory of Open Access Journals), AJOL (African Journals Online), and Cochrane Library using relevant BOOLEAN strings from our inclusion and exclusion criteria. The search on PubMed was carried out using a combination of Medical Subject Headings (MeSH) and free-text entries in the search string, such as ("Human Papilloma Virus" OR "HPV" AND ("Oropharyngeal Carcinoma" OR "Pharyngeal Carcinoma" AND ("Africa"). The search included studies published prior to 13th March, 2025-

Supplementary file. Additionally, the reference list of all relevant studies was searched based on the eligibility criteria to identify additional studies for the review.

Eligibility Criteria (Inclusion and Exclusion Criteria)

Only original research studies were eligible for inclusion. The study employed the CoCoPop (Condition, Context, Population) framework to guide eligibility criteria:

- Condition: Oropharyngeal carcinoma associated with HPV.
- Context: Studies conducted in Africa.
- Population: Individuals diagnosed with oropharyngeal carcinoma.

Outcomes of interest included prevalence, HPV subtype distribution, reported risk factors, and (where available) treatment modalities and outcomes.

Studies had to be published in English, peer-reviewed, and provide extractable data. Studies reported in other languages, qualitative studies, preprints, reviews, editorials, commentaries, conference abstracts, and grey literature were excluded.

Study selection
Two independent reviewers (A.E.B. and V.S.) screened titles and abstracts to determine eligibility following the predetermined inclusion and exclusion criteria registered in the PROSPERO protocol after article duplicates were removed using the Rayyan tool.[8] Eligible studies were subjected to a full-text review independently by A.E.B. and V.S., and disagreements were resolved through discussion and involvement of a third reviewer (O.B.).

Data extraction
Data extraction was performed independently using Excel Spreadsheets (Version 2401) by two researchers (V.S. and A.E.B.), who gathered relevant information from the included papers that met the requirements of a pre-agreed extraction form for consistency. Extracted data included the author's name, year of publication, study design, sample size, population characteristics, HPV detection method, prevalence, HPV subtype, treatment modalities, outcomes, follow-up duration, and study limitations.

Quality assessment
Two authors (V.S. and A.E.B) independently evaluated the quality of the included studies using the ROBINS-E tool.[9] The ROBINS-E tool analyses the risk of bias across seven domains, including confounding, measurement of exposure, selection of participants, post-exposure interventions, missing data, measurement of outcome, and selection of reported results for observational studies. Low risk was given when all domains are rated as low risk or, at most, two domains were moderate risk. Moderate risk was when no more than three domains were moderate risk, and high risk was given when one or more domains were adjudged high risk.

Data synthesis and statistical analysis
The study selection process was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. As illustrated in the PRISMA flow chart (Figure 1), the initial search yielded a total of 855 records across multiple databases. Following the removal of 303 duplicate records, 552 records remained for title and abstract screening, of which 499 were excluded on the basis of irrelevance to the review question. A total of 53 full-text articles were retrieved for eligibility assessment. Of these, 38 were excluded for the following reasons: wrong population (n=12), wrong outcome (n=10), wrong study design (n=8), and insufficient data for meta-analysis (n=8). Fifteen studies ultimately met all eligibility criteria and were included in the final quantitative synthesis.

For each included study, the number of HPV-positive oropharyngeal carcinoma cases and the total number of oropharyngeal carcinoma cases examined were extracted to compute a crude prevalence proportion. These proportions served as the primary effect measure for the meta-analysis. Where studies reported prevalence across multiple head and neck subsites, only oropharyngeal-specific data were extracted to maintain consistency with the review question. Study-level moderator variables extracted for subgroup and meta-regression analyses included: country of study, study design (cross-sectional or retrospective), HPV detection method (PCR-based, p16 immunohistochemistry, or a combined approach), and mean patient age.

Given the anticipated clinical and methodological heterogeneity across studies conducted in different African countries using varied HPV detection platforms, a random effects model was selected for pooling of prevalence estimates. This model accounts for both within-study sampling variation and between-study variance ($\hat{o}^2$), producing a pooled estimate that is more generalisable across the range of populations represented.

Heterogeneity across studies was quantified using the I^2 statistic and Cochran's Q test. Four meta-regression analyses were conducted to investigate whether pre-specified moderator variables could explain the observed between-study heterogeneity. Results are presented as bubble plots (Figures 5–8), in which each bubble represents a study, with bubble size proportional to study weight in the meta-analysis. Publication bias was assessed using a funnel plot of study effect sizes against their standard errors.

RESULTS
As presented in Figure 1, 126 studies were initially identified. After removal of duplicates and screening, 15 studies involving a total of 896 oropharyngeal samples met the inclusion criteria and were included in the meta-analysis. The PRISMA flow diagram (Figure 1) details papers screened, duplicates removed, and reasons for exclusion. The specific details of the 15 studies are summarized in Table 1.[10-24]

Study characteristics
The 15 included studies, conducted between 2012 and 2022 across 10 African countries (Nigeria, South Africa, Sudan, Kenya, Ghana, Uganda, Malawi, Senegal, Cameroon, Mozambique), were largely cross-sectional or retrospective analyses of archival tissue. From the cumulative sample size of 2,400 in these studies, 896 oropharyngeal cancer samples were identified and formed the sample size of this meta-analysis. As presented in Table 1, the sample sizes of each of the

Table 1: Characteristics of 15 studies included to assess prevalence, treatment and outcomes of HPV associated Oropharyngeal cancers in Africa

Study ID	Author	Year	Study Design	Location	Study Size	Population Characteristics	HPV Detection Method	HPV Prevalence in total sample	Prevalence of HPV associated Oropharyngeal CA	HPV Subtype	Treatment Modalities	Outcome Measured	Follow-up Duration	Key Findings	Limitations
1	Benjamin Idemudia Akhiwu et al [7]	2021	Cross-sectional study	Nigeria	41 patients	Gender: M: 73.2% (30/41), F: 26.8% (11/41); Age range: 21-70 +, mean 61.6 ± 11.0	Real-time PCR using the HPV Genotypes 14 Real-TM Quant kit	17.1% (7/41)	17.1% (7/41) – All cases were oropharyngeal carcinomas (OPC) Males - 4 (57.1) Females - 3 (42.9	HPV 16 - 3 (42.9%) HPV 33 - 1 (14.3%) HPV 52 - 1 (14.3%) HPV 16,33 - 1 (14.3%) HPV 33,35 - 1 (14.3%)	N/A (no treatment details provided)	Prevalence and genotype distribution of high-risk HPV in oropharyngeal carcinoma	N/A	Prevalence of HPV was 17.1% with a male to female ratio of 2.7: 1. The identified genotypes were 16, 33, 35 and 52 with 28.6% of patients having more than one genotype. Most of the age groups studied were affected. Squamous cell carcinoma and ameloblastic carcinoma were the cancers associated with HPV. HPV was not identified in the HIV positive patients.	This study has a few limitations, which could be taken into consideration in a larger study. They include the small sample size resulting from the major challenge of getting enough cases within the limited study period. Control subjects were not sampled to determine prevalent HPV genotypes in subjects without OPC and the low number of subjects with HIV to ascertain the role of HIV in OPC in a Nigeria population
2	Atang Bulane et al [8]	2020	Retrospective study	South Africa	780 samples	Gender: M: 80.9% (631/780), F: 19.1% (149/780); Age (HPV+): Mean ~55.5 years (range 29–86, varies by site)	Nested PCR targeting the L1 gene followed by an in-house hemi-nested PCR for the E6 gene and sequencing	7.3% (57/780)	10.8% (13/120 oropharyngeal carcinomas)	HPV16 (45.6%), HPV6 (17.5%), HPV18 (3.5%), HPV31/33/35/45/52/59 (1.8%–5.3%)	N/A (no treatment details provided)	Detection of HPV DNA in HNSCC and distribution of HPV types by anatomical site	N/A	The overall HPV DNA prevalence in HNSCCs was low (7.3%), with the highest prevalence in sinonasal (16.0%) and oropharyngeal (10.8%) cancers, and HPV16 predominated.	Reliance on FFPE tissues (potential DNA degradation), no oncogene expression analysis to confirm causality.
3	Fatima E. Mohamed et al [9]	2021	Cross-sectional study	Sudan	150 patients	Gender: M: 53.3% (80/150), F: 46.7% (70/150); Age range: 18–87 years (mean: 48.8 ± 11.9)	Polymerase Chain Reaction (PCR) targeting HPV-16 DNA	17.3% (26/150)	0% (0/6 oropharyngeal carcinomas)	HPV-16 (sole focus of the study)	N/A (no treatment details provided)	Prevalence of HPV-16 across various carcinoma types	N/A	HPV-16 prevalence: 15% in esophageal SCC (14/40), 50% in laryngeal SCC (6/12), 0% in oropharyngeal carcinoma. No association with gender.	Small sample size for specific cancer types (e.g., oropharyngeal n=6), lack of prognosis data, and focus on HPV-16 only (no other subtypes tested).
4	Joyce Aswani et al [10]	2019	Cross-sectional study	Kenya	160 patients	Gender: M: 73.1% (117/160), F: 26.9% (43/160); Age range: 16–87 years (mean: 51.6, median: 54)	Real-time PCR targeting 14 high-risk HPV genotypes	7.5% (12/160)	0% (0/8 oropharyngeal carcinomas)	HPV56 (83.3%), HPV52 (8.3%), HPV35 (8.3%)	N/A (no treatment details provided)	Clinicopathological predictors of high-risk HPV among HNSCC patients	N/A	Low HPV prevalence (7.5%) in HNSCC; HPV56 dominant. No HPV16/18 detected. No association between HPV+ status and typical risk factors (e.g., smoking, sexual behavior). Higher HPV+ rate in HIV+ patients (20% vs. 6.7% in HIV–).	Small sample size for specific tumor sites (e.g., oropharynx n=8, no HPV16/18 detected (contrary to global trends), reliance on PCR without oncogene expression analysis. Results were not confirmed with molecular techniques (e.g., PCR or ISH)
5	Hussan Gadelkarim Ahmed et al [11]	2012	Retrospective study	Sudan	150 patients	Gender: M: 60% (90/150), F: 40% (60/150); Age range: 12–85 years (mean: 54)	p16 immunohistochemistry (IHC)	20.7% (31/150)	N/A (Study combined multiple head/neck sites; oropharyngeal CA not specified)	N/A (Subtype not genotyped; p16 used as surrogate marker)	N/A (no treatment details provided)	Determination of HPV attribution in head and neck cancers using p16 overexpression	N/A	20.7% of HNSCCs were HPV+ (p16-positive). HPV+ cases most common in oral cancers (35.4% of HIV+ cases). HPV prevalence higher in males (58%) and age groups 31–40 years (32%). Study highlights HPV's role in HNSCCs in Sudan but lacks subtype data.	
6	Gloria Dapaah et al [12]	2022	Retrospective study	South Africa	266 patients	Gender: M: 80% (213/266), F: 20% (53/266); Mean age: 57.6 years (HPV+ subgroup: 33–72 years)	p16 immunohistochemistry (IHC) for screening, followed by BD Onclarity PCR assay for high-risk HPV genotyping	5% (13/266)	5% (13/265) – All HPV+ cases were oropharyngeal squamous cell carcinomas (OPSCC)	HPV-16 (10/13), HPV-18 (1/13), HPV-52 (1/13), HPV-31 (1/13); 1 case co-infected with HPV-16/31.	6 Patients treated. Radiotherapy = 3 Radiotherapy + Chemotherapy = 3	Survival and recurrence (partial data: 1 death, 1 recurrence, 4 disease-free)	N/A	HPV prevalence in OPSCC was 5%, suggesting HPV is a minor etiologic agent in this region. p16 IHC had low positive predictive value (36.1%); HPV-specific testing is recommended. Identification of less common HPV subtypes (HPV-52, HPV-31) highlights potential gaps in bivalent vaccination coverage. HPV− cases were younger (mean age: 5_ years) and predominantly non-keratinizing (10/13).	Only 6/13 HPV− cases had treatment information.

Table 1: Characteristics of 15 studies included to assess prevalence, treatment and outcomes of HPV associated Oropharyngeal cancers in Africa - Cont'd

7	Eleni M. Rettig et al [13]	2019	Retrospective case series	Cameroon	131 cases (11 oropharyngeal)	HNSCC cohort 74% male, median age 59 (IQR 50-68)	p16 immunohistochemistry followed by HPV-specific testing (PCR) on available OPSCC specimens	OPSCC: 29% (2/7 tested) positive	2/7 OPSCCs (29%) were HPV+ (p16 and RNA ISH positive)	OPSCC subtypes: N/A (high-risk types detected via RNA ISH, no specific genotyping)	No treatment details	Prevalence and characteristics of oral HPV infection and the HPV status of OPSCC in the region	N/A	Low oral HPV prevalence (5%) among HIV− individuals. OPSCCs comprised 8% of HNSCCs, with 29% HPV+. HPV-driven OPSCC is rare in rural Cameroon, likely due to low tobacco use and infrequent oral sexual practices.	
8	Evans Aboagye et al [14]	2019	Retrospective cross-sectional study	Ghana	100 HNSCC cases	Gender: M: 70%, F: 30%; Age: Mean 52.36 years (median 56)	Nested multiplex PCR (E6/E7 oncogenic DNA detection)	18% (18/100)	50% (6/12 oropharyngeal cancers)	HPV-16 (94.4%, 17/18) HPV-16/18 coinfection (5.6%, 1/18)	No treatment details	Presence and distribution of HPV genotypes in HNSCC cases, with emphasis on anatomical site differences	N/A	HPV-16 was dominant (94.4% of HPV+ cases). HPV prevalence highest in oropharyngeal cancers (50%). Males had higher HPV+ rates (83.3% of HPV+ cases). HPV prevalence in HNSCC aligns with prior studies in sub-Saharan Africa.	
9	Jamilah Nabukenya et al [15]	2018	Cross-sectional study with clinical follow-up	Uganda	51 HNSCC patients	Gender: M: 86.2% (44/51), F: 13.5% (7/51); Age: 20–90 years (mean 57.7 ± 14.0)	p16 immunohistochemistry (IHC) on tumor biopsies	11.8% (6/51)	9.8% (5/51; HPV+ cases in oropharyngeal subsite)	HPV16 (100% of HPV+ cases)	N/A (No treatment details beyond biopsy/serology; no radiotherapy due to cost)	1-year survival rate (4%), HPV prevalence, staging, tumor differentiation	1-year survival data provided	80.1% presented with late-stage HNSCC. - HPV16 prevalence: 11.8%. - 1-year survival: 4%. - Late-stage associated with low socioeconomic status and delayed hospital presentation.	Genetic assays were not performed due to financial constraints.
10	Claire E. Faggons et al [16]	2017	Descriptive study	Malawi	77 HNSCC cases	Gender: M: 65% (50/77), F: 35% (27/77); Age: Mean 52.4 years (SD 16.8)	p16 immunohistochemistry (IHC)	17% (7/42) among tested cases	22% (5/23) in OP/OC tumors	N/A (subtypes not specified; p16 used as surrogate for HPV association)	N/A (no treatment details provided; radiotherapy scarce due to resource limitations)	Association between p16 positivity (as a surrogate for HPV) and tumor site, alongside evaluation of risk factors	N/A	HPV-associated HNSCC is uncommon in Malawi (17% p16+). 22% of OP/OC tumors were HPV-associated. Low HPV prevalence despite high cervical cancer burden. Limited association with HIV, tobacco, or alcohol use.	Small sample size, missing data (e.g., substance use, HIV status), and lack of tumor subtype differentiation.
11	Cathy Ndiaye et al [17]	2015	Cross-sectional study	Senegal	117 cases	Gender: M: 70.9% (83/117), F: 29.1% (34/117); Age: Mean 52 years (SD ±18.3)	SPF-10 PCR followed by a DNA enzyme immunoassay (DEIA) for HPV-DNA detection, LiPA25 for genotyping, and p16 immunohistochemistry (IHC) in HPV-positive cases	3.4% (4/117)	0% (0/5 oropharyngeal tumors)	HPV16 (1 case), HPV33 (1 case), HPV45 (2 cases)	N/A (no treatment details provided)	Prevalence of HPV-DNA in HNC and evaluation of its oncogenic role via p16INK4a expression	N/A (cross-sectional design)	HPV-DNA prevalence in HNC in Senegal is very low (3.4%), and none of the HPV-positive cases showed p16INK4a overexpression; suggesting that HPV is not a strong risk factor for HNC in this region.	Small sample size, lack of risk factor data, and archival record losses.
12	Jeffrey Blumberg et al [18]	2015	Retrospective study	Mozambique	51 patients	Gender: Oropharyngeal SCC: 55.2% female; Oral tongue SCC: 32.2% female. Age: N/A (data incomplete in provided text)	p16 immunohistochemistry (IHC) and HPV-16 E6/E7 PCR	0% (0/51; no HPV detected by PCR)	0% (0/22 oropharyngeal SCC)	N/A (no HPV detected via PCR)	N/A (not discussed in provided text)	HPV presence via p16 IHC and HPV-16 PCR	N/A (retrospective design)	No HPV-positive oropharyngeal or oral tongue SCC detected. Contrasts with high HPV-driven cervical cancer rates in Mozambique. Cultural/economic factors may explain absence of HPV-related HNSCC.	
13	Tumelo R. Sekoe et al [19]	2013	Cross-sectional study	South Africa	112 patients	Gender: M: 91.1% (102/112), F: 8.9% (10/112); Age range: 37.3–85.2 years	Three PCR assays (MY09/11, GP5+/6+; PGMY09/11, GP5+/6+; multiplex hemi-nested PCR targeting E6 gene) and p16 immunohistochemistry	6.3% (7/112)	5.0% (1/20 oropharyngeal cases)	HPV11, 16, 18, 31, 45 HPV16 in oropharynx and nasopharynx; HPV18 in nasopharynx; HPV31, 45 in larynx; HPV11 in hypopharynx	N/A (not discussed)	HPV prevalence, genotype distribution, association with p16 staining	N/A (cross-sectional design; no follow-up reported)	HPV prevalence: 6.3% (7/112). HPV16, 18 31, 45 detected. Moderate agreement between HPV DNA and p16 staining. HPV-negative p16-positive tumors may have worse prognosis.	
14	C L Davidson et al [20]	2014	Cross-sectional study	South Africa	125 participants	Gender: M: 100% (125/125); Age range: 17-64 years (median 50)	Linear Array HPV Genotyping Test (Roche Molecular Systems); oral rinse/gargle samples; questionnaire; optional HIV testing	5.6% (7/125)	5.6% (7/125) of total participants (no cancer cases reported)	HPV16 (1 case), HPV68 (1 case), HPV71, HPV72 (co-infection in 1 case), HPV55, HPV70, HPV72 (single infections)	N/A (prevalence study; no treatment data reported)	HPV prevalence, association with sexual behavior, substance use, HIV status, and clinical mucosal pathology	N/A (cross-sectional design)	Low oral/oropharyngeal HPV prevalence (5.6%) in South African men. Significant association with multiple lifetime sexual partners (p = 0.027). High-risk HPV16/68 found in 2/7 HPV+ cases. No link to HIV, substance use, or clinical lesions. Oral sex uncommon, but both hrHPV cases reported oral sex.	
15	C. Kabu et al [21]	2014	Retrospective review	Ghana	78 cases	Gender: M: 74.4% (58/78), F: 25.6% (20/78); Age range: 22-92 years (mean 57.92)	Nested multiplex PCR for HPV-DNA genotyping	19.23% (15/78)	Oral cavity: 13.8% (4/29), Pharynx 18.2% (2/11)0%	HPV16 (80%, 12/15) HPV18 (13.3%, 2/15), HPV16+18 co-infection (6.7%, 1/15)	N/A (study focused on HPV prevalence, not treatment)	Prevalence and genotype distribution of HPV-DNA in HNSCC specimens from Ghana	N/A (retrospective analysis)	HPV16 predominant (86.7%); HPV+ HNSCCs more common in males (24% vs. 5% females) and laryngeal sites (24.2%). Trend toward younger patients (<58 years) having HPV+ tumors. No HPV detected in tonsillar cancers.	Small sample size; HPV causality not confirmed (p16 staining or viral integration not assessed).

15 studies ranges from 41 to 780, with a male predominance in the fifth to sixth decades of life. HPV detection methods varied across the studies, with PCR-based assays being predominant, followed by p16 immunohistochemistry (IHC) either alone or combined with PCR (Polymerase Chain Reaction). This resulted in variable specificity and reported prevalence, which ranged from 0% in smaller studies from Sudan, Kenya, Senegal, and Mozambique, to 5–10% in several South African cohorts, 17–29% in Nigeria and Cameroon, and up to 50% in a small Ghanaian study.[10-24] HPV-16 was consistently the predominant subtype, accounting for more than 70% of typed infections, while other high-risk types (18, 31, 33, 35, 45, 52, 56) and occasional low-risk or uncommon types (6, 11, 68, 70, 72), including some co-infections, were reported.[10-24] There was sparse treatment and survival data, with a study reporting the treatment of just 6 of the 266 patients that were included in their study (3 radiotherapy and three chemoradiotherapy).[15] They went on to state that out of the six treated patients, one died, one experienced recurrence, and four were disease-free. Additionally, Nabukenya *et al.* (2018) reported a one-year survival rate in 4% of their participants.[18]

It is important to note that small OPC subsets, inconsistent diagnostic methods, and scarce outcome reporting limited the evidence. There were also geographic gaps, particularly in North and Central Africa, contributing to the high heterogeneity observed in pooled prevalence estimates.

Prevalence of HPV-Associated oropharyngeal carcinoma

Across the 15 studies on HPV-associated oropharyngeal cancers in Africa, findings demonstrate marked regional variation in prevalence, dominant subtypes, and methodological approaches (Table 1). In West Africa, studies from Nigeria, Ghana, and Senegal show mixed but generally moderate HPV prevalence. In Nigeria, a study reported a 17.1% HPV prevalence among 41 patients, confined to oropharyngeal carcinomas, with HPV16 as the dominant subtype and no detection among HIV-positive individuals, though the study was limited by small sample size and lack of controls.[10] In Ghana, an included study found an overall HPV prevalence of 18%, but a notably high rate of 50% (6/12) in oropharyngeal cancers, with HPV16 accounting for 94.4% of positive cases, representing

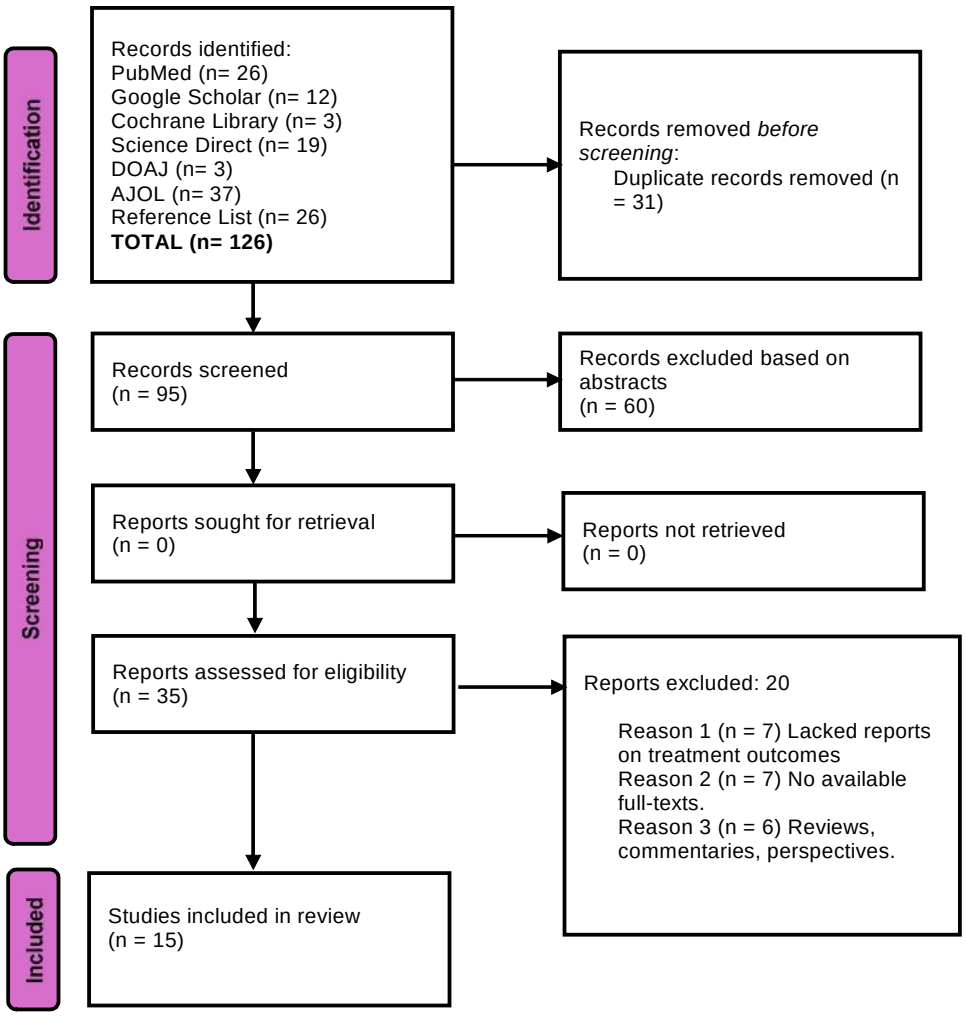

Figure 1: Prisma Flow Chart

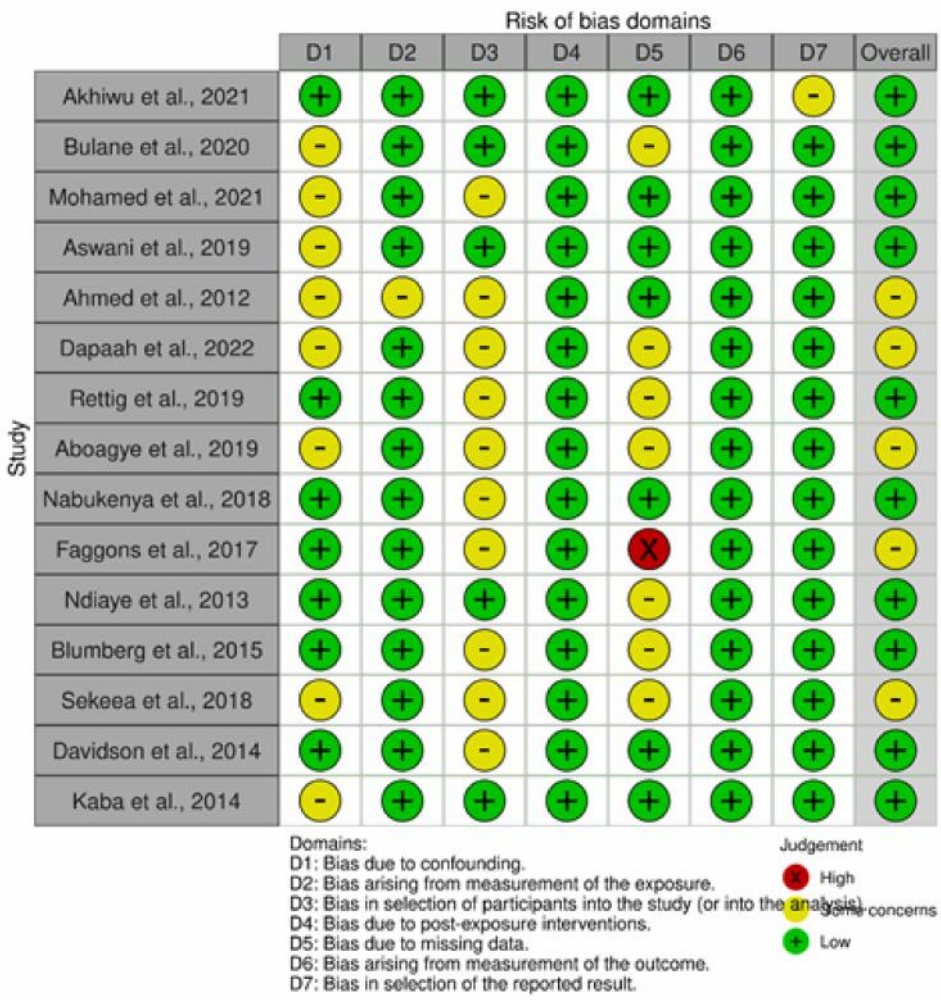

Figure 2: Risk of bias assessment

one of the highest site-specific prevalences reported.[17] Similarly, a study reported an overall HPV prevalence of 19.2% among 78 cases, predominantly HPV16 (80%), with higher rates in males and laryngeal cancers; however, no HPV was detected in tonsillar cancers, and causality was not confirmed due to lack of p16 staining and viral integration analysis.[24] In contrast, a study in Senegal, using robust detection methods (SPF-10 PCR, genotyping, and p16 IHC), reported a very low HPV prevalence of 3.4%, with no HPV detected in oropharyngeal tumours and no p16 overexpression in HPV-positive cases, suggesting a limited oncogenic role of HPV in that population.[20]

In East Africa, findings from Kenya and Uganda generally indicate low HPV prevalence in oropharyngeal cancers, with some notable epidemiological insights. An included study carried out in Kenya reported an overall HPV prevalence of 7.5% among 160 HNSCC patients, with no HPV detected in oropharyngeal cases and an unusual predominance of HPV56 rather than HPV16 or HPV18, alongside higher HPV rates in HIV-positive individuals (20% vs. 6.7%).[13] In Uganda, a study reported an HPV prevalence of 11.8% among 51 patients, all involving HPV16, and highlighted a critically low 1-year survival rate of 4%, with 80% of patients presenting at advanced stages due to socioeconomic barriers and delayed healthcare access; however, financial constraints limited the use of more advanced genetic assays.[18]

In North Africa, represented by studies from Sudan, results show variability depending on detection methods and cancer sites. A study reported an HPV-16 prevalence of 17.3% among 150 patients but found no HPV positivity among the six oropharyngeal carcinoma cases, with higher prevalence observed in oesophageal (35%) and laryngeal (50%) cancers; interpretation was limited by the small oropharyngeal subgroup and focus on a single HPV subtype.[12] In contrast, a 2012 study using p16 immunohistochemistry as a surrogate marker without molecular confirmation, reported a higher HPV positivity rate of 20.7%, particularly in oral cancers and among males aged 31–40 years, though the absence of PCR-based validation limits the reliability of these findings.[14]

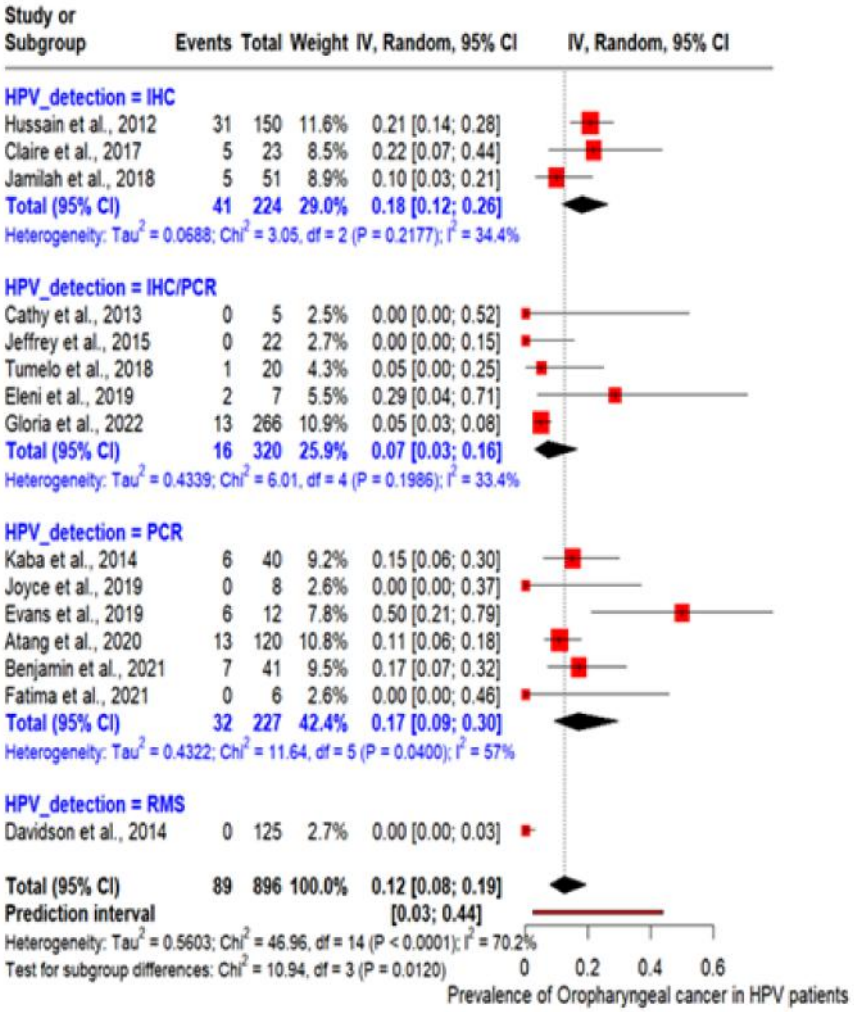

Figure 3: Forest plot analysis by detection method

In Central Africa, limited data from Cameroon suggests that HPV-driven oropharyngeal cancer is relatively uncommon. A study, in a retrospective case series of 131 HNSCC cases, found that 2 out of 7 (29%) oropharyngeal cancers were HPV-positive using both p16 IHC and RNA in situ hybridization. The authors concluded that HPV-associated disease is rare in rural settings, potentially due to lower tobacco use and less frequent oral sexual practices.[16]

In Southern Africa, which contributed the largest number of studies, HPV prevalence in oropharyngeal cancers is generally low, though findings vary by methodology and population. A 2020 study reported a low overall HPV DNA prevalence of 7.3% among 780 HNSCC samples, with slightly higher rates in oropharyngeal cancers (10.8%) and HPV16 as the dominant subtype, though FFPE tissue use posed limitations.[11] Moreover, a study found an even lower prevalence of 5% among 266 patients, with all HPV-positive cases occurring in oropharyngeal squamous cell carcinomas and HPV16 present in most (10/13), while also demonstrating the poor positive predictive value of p16 (36.1%) and limited treatment data availability.[15] A 2018 study had earlier reported, using multiple PCR assays alongside p16 IHC, a prevalence of 6.3%, with only 1 of 20 oropharyngeal cases positive and multiple HPV genotypes detected[11,16,18,31,45], and further noted that HPV-negative but p16-positive tumours may have worse prognosis.[22] In Mozambique, a study reported no HPV detection in any of the 22 oropharyngeal carcinoma cases (0%), despite the country's high cervical cancer burden, suggesting differing transmission dynamics.[21] In Malawi, an included study found p16 positivity in 17% of cases, with 22% of oropharyngeal/oral tumours being HPV-associated, though overall HPV contribution to head and neck cancers remained limited.[19] Additionally, a 2014 study in a non-cancer cohort of 125 healthy South African men, reported an oral/oropharyngeal HPV prevalence of 5.6%, significantly associated with multiple lifetime sexual partners, with HPV16 and HPV68 detected in individuals reporting oral sex and no association with HIV or substance use.[23]

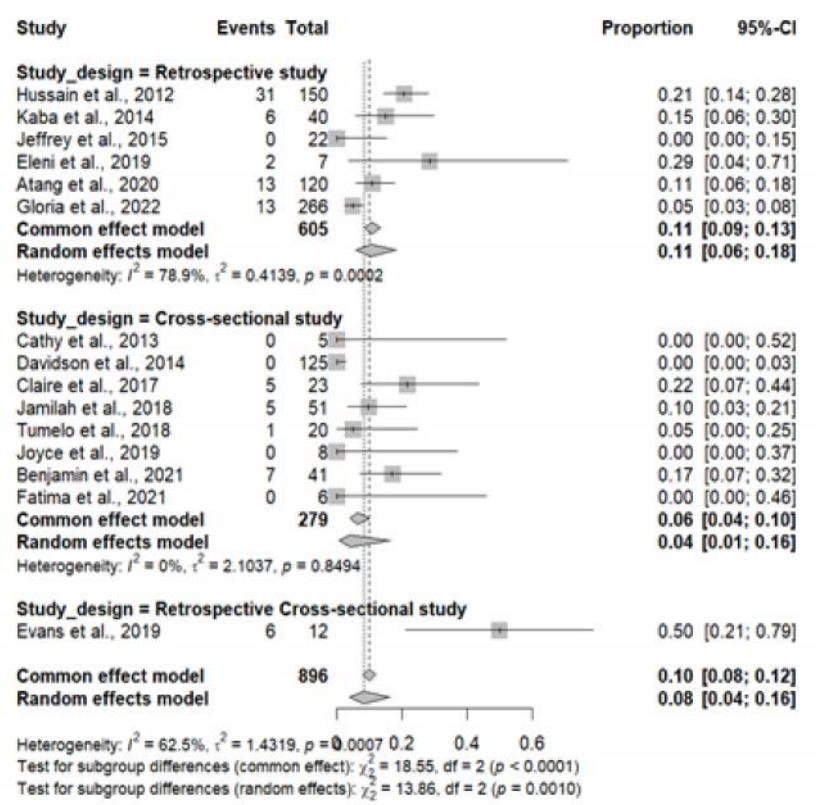

Figure 4: Forest plot analysis by study design

Across all regions, HPV prevalence in oropharyngeal cancers in Africa remains generally lower than that reported in Western populations, with HPV16 consistently identified as the predominant subtype where present. However, substantial variability exists across regions and studies, largely influenced by differences in detection methods, sample sizes, and population characteristics, and most studies are further limited by insufficient data on treatment outcomes and survival.

Characteristics of HPV-Associated oropharyngeal carcinoma

The forest plot **(Figure 3)** illustrates a subgroup meta-analysis of oropharyngeal cancer prevalence among HPV-positive patients, stratified by HPV detection methods. Overall, the pooled prevalence across the 15 studies revealed a prevalence rate of 12% (95% CI: 8%–19%), with significant heterogeneity (I^2 = 70.2%). In subgroup analysis, studies using IHC alone reported the highest pooled prevalence at 18%,

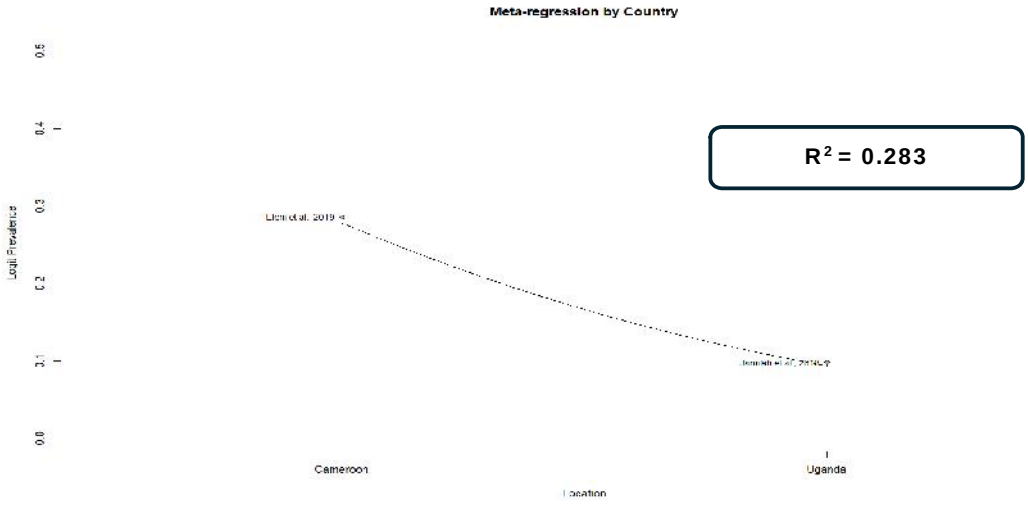

Figure 5 : Meta-regression by country

The bubble plot shows a meta-regression with an R^2 = 0.283, indicating that about 28.3% of between-study heterogeneity is explained by the moderator. The spread of points around the regression line suggests a moderate explanatory power.

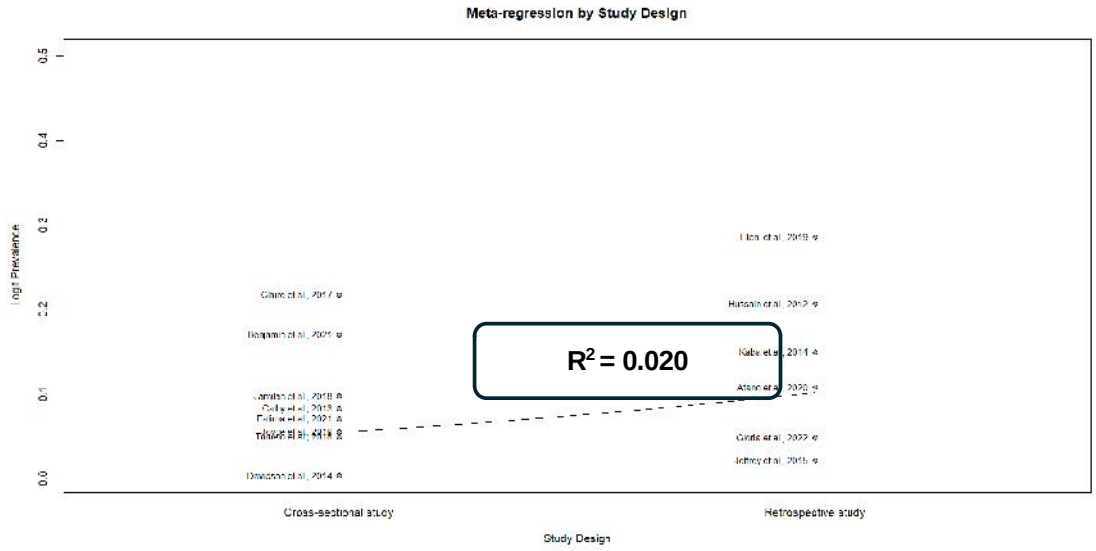

Figure 6: Meta-regression by study design

The bubble plot presents R² = 0.020, meaning only 2% of the heterogeneity is explained. This shows that the moderator variable here has minimal predictive value for between-study differences.

followed by PCR at 17%, and IHC/PCR at 7%. Only one study used RMS (Roche Molecular Systems), reporting 0% prevalence.[23] The test for subgroup differences was statistically significant (Chi² = 10.94, p = 0.012), indicating that detection methods may influence reported prevalence rates. Moderate heterogeneity was observed within each subgroup.

are illustrated in Figures 5–8. The country-level meta-regression (Figure 5) showed that geographic setting explained approximately 28.3% of between-study heterogeneity (R^2 = 0.283), with West African studies contributing to higher prevalence estimates compared to those from Southern and Eastern Africa. In contrast, study design as a moderator (Figure 6) accounted for

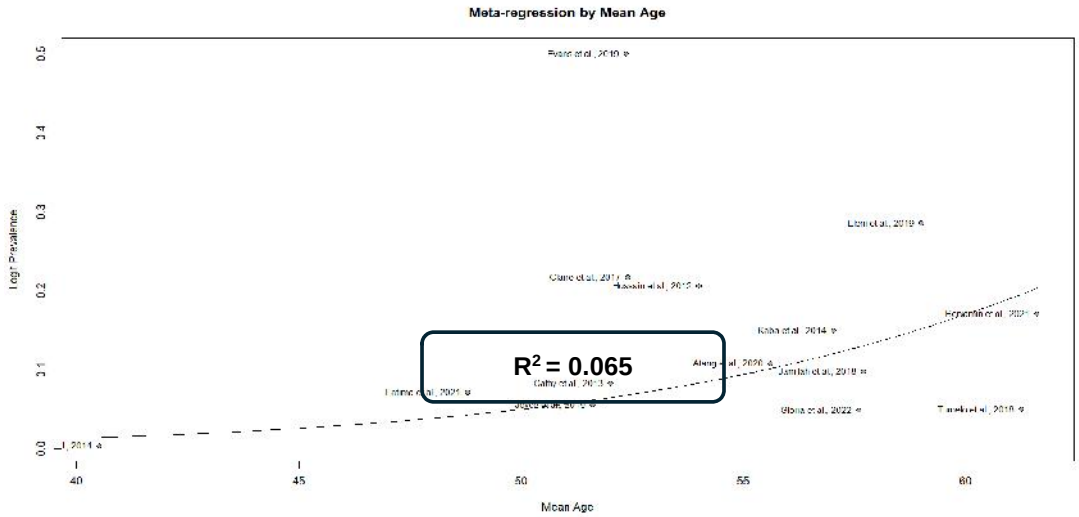

Figure 7: Meta-regression by mean age

The regression line here corresponds to R² = 0.065, indicating that just 6.5% of the heterogeneity is accounted for. While there is some explanatory value, most variability remains unexplained.

These highlight the potential impact of diagnostic methods on outcome estimates.

As presented in Figure 4, stratification by study design revealed that cross-sectional studies tended to report the highest pooled prevalence estimates. Further analyses

only 2% of heterogeneity (R^2 = 0.020), indicating minimal explanatory value.

Participants' mean age (Figure 7) explained 6.5% of between-study variability (R^2 = 0.065), with a trend toward higher HPV positivity in younger cohorts (not

statistically significant). The detection method (Figure 8) also explained 6.5% of heterogeneity ($R^2 = 0.065$), supporting subgroup findings that reliance on p16 IHC tended to overestimate prevalence relative to PCR-based or combined approaches.

Regional subgrouping (Figure 9) suggested West African studies tended to report higher prevalence than Southern or Eastern Africa, though small sample sizes (less than 10 OPC cases) limit conclusions.

Treatment outcome

Across the studies reviewed, treatment and outcome data on HPV-associated oropharyngeal cancers in Africa were notably sparse, as the majority of studies were designed as prevalence or epidemiological investigations focused primarily on HPV detection rather than clinical management. Only one of the studies, one from South Africa, reported any treatment-related information, and even this was limited to just 6 of the 13 HPV-positive patients. Among these, three

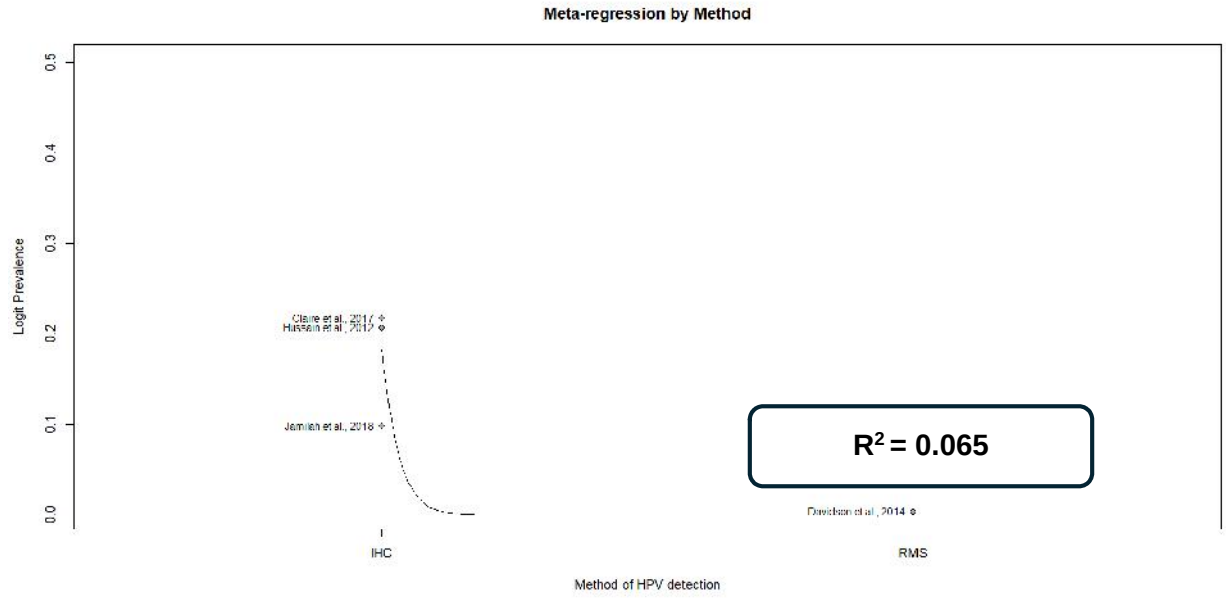

Figure 8: Meta-regression by detection method

Similar to Figure 7, with $R^2 = 0.065$, the plot demonstrates a weak moderator effect. The bubble distribution around the regression line suggests only limited influence of the studied factor on outcome variability.

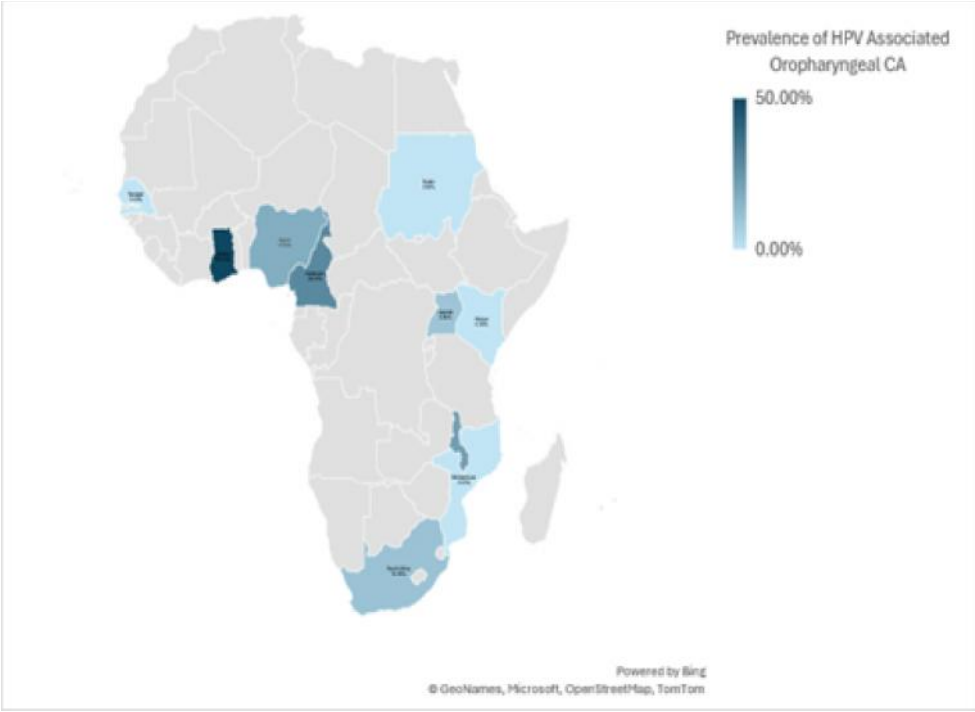

Figure 9: Representation of prevalence of HPV associated oropharyngeal CA by country

patients received radiotherapy alone, while the remaining three underwent a combination of radiotherapy and chemotherapy.[15] Reported outcomes for these six patients included one death, one recurrence, and four who were disease-free; however, no additional details were provided regarding follow-up duration, treatment dosing, or standardized response metrics, limiting interpretation of these outcomes. Separately, the Ugandan study was the only study to provide survival data, documenting an extremely low 1-year survival rate of 4% among 51 HNSCC patients, despite not reporting specific treatment modalities.[18] This poor outcome was contextualized by the finding that 80% of patients presented at advanced stages of disease, with most unable to access radiotherapy due to financial constraints, reflecting broader systemic challenges such as low socioeconomic status and delayed healthcare presentation.

Risk of bias assessment

Risk of bias as presented in **Figure 2** was assessed for all 15 included studies using the ROBINS-E (Risk of Bias in Non-randomised Studies of Exposures) tool, which evaluates seven domains: bias due to confounding (D1), bias arising from measurement of the exposure (D2), bias in selection of participants into the study (D3), bias due to post-exposure interventions (D4), bias due to missing data (D5), bias arising from measurement of the outcome (D6), and bias in the selection of the reported result (D7).

Bias due to confounding (D1) was rated as low in seven studies and some concerns in eight. Studies rated as some concerns in this domain were predominantly retrospective in design, with no adjustment for established confounders such as tobacco use, alcohol consumption, HIV status, or sexual behaviour, all of which are recognised risk factors for both HPV infection and head and neck squamous cell carcinoma. Studies by Akhiwu *et al.* (2021), Rettig *et al.* (2019), Nabukenya *et al.* (2018), Faggons *et al.* (2017), Ndiaye *et al.* (2013), Blumberg *et al.* (2015), and Davidson *et al.* (2014) were rated low in this domain, reflecting more systematic sampling approaches or prospective designs that mitigated confounding concerns.

Bias from measurement of the exposure (D2) was rated low across the majority of studies, with some concerns identified only in Ahmed *et al.* (2012). This reflects the generally consistent use of validated HPV detection methods across studies, including polymerase chain reaction (PCR)-based assays and immunohistochemistry (IHC). The concern in Ahmed *et al.* (2012) arises from reliance solely on p16 immunostaining without molecular confirmation, which limits the precision of exposure ascertainment.

Bias in selection of participants (D3) was rated as some concerns in the majority of studies (ten of fifteen), and low in only five; Akhiwu *et al.* (2021), Bulane *et al.* (2020), Aswani *et al.* (2019), Ndiaye *et al.* (2013), and Kaba *et al.* (2014). The predominant concern across studies was the use of archival formalin-fixed paraffin-embedded (FFPE) tissue, which introduces potential DNA degradation and sample attrition, alongside single-centre recruitment and hospital-based sampling that may not represent the broader population of patients with head and neck squamous cell carcinoma. Several studies also had incomplete tissue availability for HPV testing, further limiting the representativeness of the analytic sample.

Bias due to post-exposure interventions (D4) was rated low for all 15 studies. Given that the included studies were predominantly observational in design with no therapeutic intervention forming part of the study protocol, this domain was consistently not applicable as a source of bias.

Bias due to missing data (D5) was the most variable domain across the included studies. Seven studies were rated low, six were rated as some concerns, and one study, Faggons *et al.* (2017), was rated high risk. The high rating for Faggons et al. reflects pervasive missing data across multiple key variables, with HIV status unknown in 55% of patients, tobacco use data missing in 48%, and alcohol use data missing in 49% of cases, all of which are variables directly relevant to the study's research question. Studies rated as some concerns in this domain typically lacked complete risk factor data or had incomplete HPV testing across all recruited participants. Studies rated low in this domain either had prospectively collected data or reported complete case ascertainment for the primary outcome of interest.

Bias from measurement of the outcome (D6) was rated low across all 15 studies. HPV status as an outcome was determined using pre-specified, objective laboratory methods in all included studies, and outcome assessors were generally blinded to other patient characteristics, reducing the risk of differential misclassification.

Bias in the selection of the reported result (D7) was rated low in 14 of 15 studies. Akhiwu et al. (2021) was rated as some concerns in this domain, reflecting the limited study period, small sample size, and the possibility that genotype reporting may have been selectively emphasised given the small number of HPV-positive cases identified.

No study was rated as overall high risk of bias. The most frequent sources of concern across the body of evidence were selection bias arising from single-centre hospital-based recruitment, measurement limitations related to the use of p16 immunohistochemistry as a sole surrogate marker for HPV without molecular confirmation, and missing data on key confounding variables. These limitations are broadly consistent with the resource-constrained settings in which the majority of studies were conducted and should be considered when interpreting the pooled findings of this review.

Publication bias and heterogeneity

Subgroup analyses revealed variation in pooled HPV prevalence estimates depending on study characteristics. Country-level subgrouping (Figure 9) showed higher pooled prevalence in West African studies (notably Ghana and Nigeria) compared to those from Southern and Eastern Africa, though these estimates were often based on small sample sizes. Subgrouping by mean age of participants suggested that studies with younger cohorts tended to report slightly higher HPV positivity, but results were not statistically significant. Meta-regression analyses demonstrated that study-level moderators explained only a limited proportion of heterogeneity: the strongest model accounted for 28.3% ($R^2 = 0.283$) of between-study variability, while others explained far less (2–6.5%).

The Egger's test for funnel plot asymmetry produced a z-value of -1.6674 with a p-value of 0.0954 (Figure 10).

Discussion

Human papillomavirus-positive (HPV+) oropharyngeal carcinomas have increased in incidence over the past decade.[25-28] This systematic review and meta-analysis summarized available African data, showing a pooled prevalence of 12% with substantial heterogeneity ($I^2 = 70.2\%$). Our estimate is comparable to the 11% pooled prevalence reported in a South African review by Wood et al., but remains lower than pooled estimates from North America (21.6%) and Europe (21.5%).[29, 30] This lower prevalence in Africa may reflect differences in sexual cultural practices, genetics, diagnostic approaches/limitations, or possible variations in viral strains.

Pooling data from 15 studies, only one study provided follow-up details.[18] Due to the late presentations observed in this study, survival after one year was only observed in 4% of the cases (18), despite HPV+ OPC having higher survival rates in global reports. This highlights the importance of routine screening, education, vaccination (prior to age 27 years), and other grassroots interventional campaigns.[31,32] While HPV+ OPCs have low associations with alcohol and tobacco, there must be organized collaborative efforts towards preventive strategies, including substance use counselling, especially since the prevalence of some high-risk behaviors is rising amongst African youths.[33, 34] Improving the survival rates of patients also involves practical management approaches. Studies included in this review reported the use of radiotherapy and chemotherapy, which aligns with best global

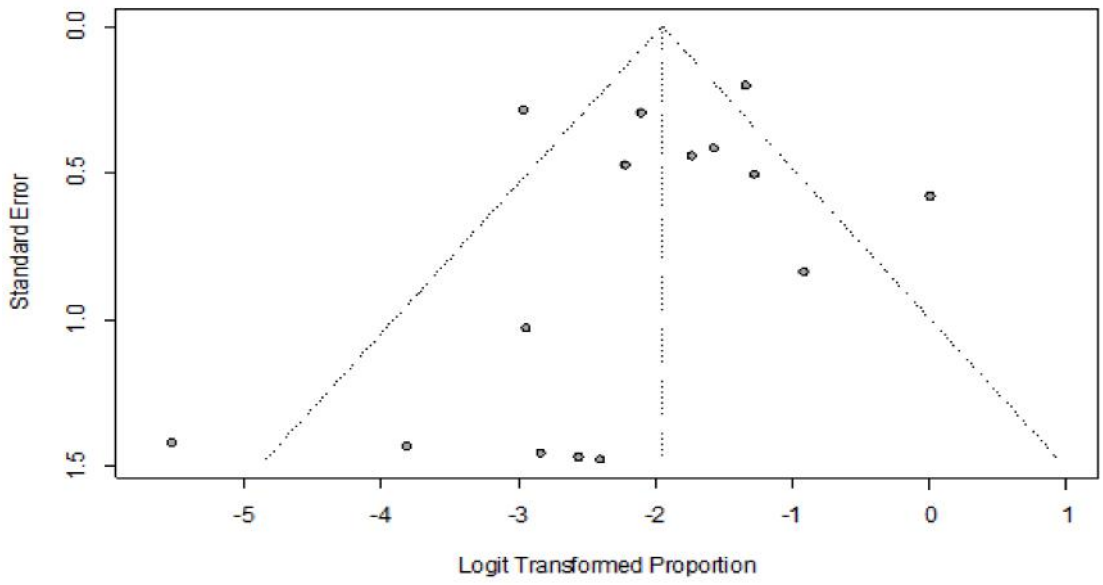

Figure 10: Funnel plot

This plot appears asymmetrical, with more data points scattered to the left of the central line and fewer on the right. This asymmetry may indicate potential publication bias, where smaller studies with non-significant or lower prevalence estimates may be underreported or unpublished. The uneven distribution suggests that the meta-analysis results should be interpreted with caution, considering the possibility of bias influencing the pooled estimates

standards.[35,36] While HPV+ tumors are reported to respond better to chemotherapy compared to HPV negative OPCs, with early presentations, patients may also benefit from surgical resections, followed by post-operative radiation (60-66 Gy) and chemotherapy.[37-39]

Diagnosis often involves complete clinical assessment, imaging, and biopsy of a primary lesion, providing a stepwise clinical, histological, and molecular approach.[31, 35] Following histopathological confirmation (a destructive squamous cell carcinoma morphology) of OPC, a distinction between HPV- (keratinizing) and HPV+ (non-keratinizing) subtypes must be made since this affects treatment approaches and prognostic estimates.[41] One of the significant findings from this review is the influence of diagnostic methods, where studies using p16 IHC alone showed a higher pooled prevalence (18%) compared to PCR (17%) or combined methods (7%). This highlights the differences between the two methods, as PCR is known to be a more specific diagnostic method.[41] Although p16 IHC is relatively less expensive, rapid, and widely available, a combination approach is recommended, as utilized in some of the studies reviewed.[41]

Meta-regression analyses provide additional insights into sources of heterogeneity. Country-level subgrouping across West Africa, Central Africa, and East Africa explained the most significant proportion of variability ($R^2 = 0.283$), with a higher prevalence generally observed in West African studies compared to those in Southern and Eastern Africa, although sample sizes were small. Study design explained only 2% of variability, while mean age (54.6 years) explained 6.5%, with a weak trend toward higher prevalence in younger populations. The detection method explained an additional 6.5% of heterogeneity, reinforcing the subgroup finding that IHC-based detection may overestimate (result in false positives) prevalence relative to molecular techniques. Collectively, these analyses indicate that while methodological and demographic factors partially contribute to heterogeneity, a large proportion remains unexplained, likely reflecting unmeasured confounders such as sexual behaviour, HIV status, and healthcare access.

Treatment data were sparse and inconsistently reported.[10-24] Only a few studies provided their management plans, treatment details, and outcome data. Dapaah et al.'s (2022) management report on six of the 266 participants is insufficient to support generalizable conclusions.[15] Thus, these findings on treatment should be considered exploratory rather than comprehensive. Moreover, some studies have alluded to the lack of infrastructure, cost constraints, and late-stage presentation as barriers to comprehensive treatment and the need for more cost-effective strategies to improve the diagnosis and management of HPV head and neck cancers in Africa.[41,42]

The strengths of the reviews involve the use of a well-planned methodological design from protocol registration to data extraction and meta-analyses. This study, however, has some limitations. We noted high heterogeneity (I2=70.2%) despite most of the studies using cross-sectional designs. Although, publication bias assessment showed no statistically significant evidence of bias by Egger's test, the funnel plot demonstrated some asymmetry, suggesting possible small-study effects. This further points to the need for cautious interpretation of pooled prevalence estimates, as underreporting of negative or low-prevalence findings cannot be excluded.

Finally, this review emphasizes the importance of standardized diagnostic protocols for HPV detection, as well as early and grassroots educational programs, increased HPV vaccination coverage, equitable access to diagnostics, and enhanced early detection and treatment infrastructure across African health systems.[43,44] We also recommend investing in registries and longitudinal follow-up, which would strengthen the evidence for public health planning. Future research should prioritize prospective, multi-country studies using standardized HPV diagnostics and follow-up.

CONCLUSION

HPV-associated oropharyngeal carcinoma is present across Africa but at a substantially lower pooled prevalence of 12% than reported in Western populations, with considerable variation driven largely by geography and diagnostic methodology. HPV-16 remains the dominant oncogenic subtype continent-wide. The detection of additional high-risk subtypes beyond HPV-16 and HPV-18 in several countries raises important questions about the adequacy of current bivalent vaccination programmes in providing comprehensive oropharyngeal cancer protection across African populations.

Additionally, the near-total absence of treatment and survival data is the most critical gap identified by this review, making it impossible to draw meaningful conclusions about clinical outcomes for HPV-positive oropharyngeal carcinoma in the African context. The limited available evidence, including a one-year survival rate of 4% in Uganda, suggests that late presentation and restricted access to treatment are as consequential as prevalence in determining patient prognosis.

Finally, realising improvements in this space will require standardised diagnostic protocols, expanded longitudinal data collection, and investment in treatment infrastructure. Prospective multi-country studies using harmonised HPV detection methods and systematic outcome reporting are urgently needed to fill the evidence gaps this review has exposed.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests

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Authors' contributions: V.S Conceptualized the study. V.S and A.E.B contributed equally to the study. V.S, A.E.B, A.O.O, O.B, O.O, K.G, V.J, O.A and T.W were involved in writing the first and final draft. V.S, A.E.B, A.O.O, O.B, O.O, K.G, V.J, O.A and T.W read and approved the final manuscript.

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