original reports abstract

Human Papillomavirus–Associated Head and Neck Malignancies in Sub-Saharan Africa: A Systematic Review

Samuel Okerosi, MBChB, MMed[1]; Lillian Wairimu Mokoh, MBChB, MMed[2]; Fidel Rubagumya, MD, MMed[3,4]; Brandon Asuman Niyibizi, BPharm[4]; Aslam Nkya, MD, MMed[5]; Katherine Van Loon, MD, MPH[6,7]; Geoffrey Buckle MD, MPH[6,7]; Stephen Bent, MD[6]; Patrick Ha, MD[7,8]; Johannes J. Fagan, MBChB, FCS, MMed[9]; Dianna Ng, MD[10]; Joyce Aswani, MMed[11]; and Mary Jue Xu, MD[7,8]

PURPOSE The proportion of head and neck cancers (HNCs) with human papillomavirus (HPV) positivity in sub-Saharan Africa (SSA) is poorly characterized. Characterizing this has implications in staging, prognosis, resource allocation, and vaccination policies. This study aims to determine the proportion of HPV-associated HNC in SSA.

MATERIALS AND METHODS This systematic review included searches from PubMed, EMBASE, Web of Science, African Index Medicus, Google Scholar, and African Journals Online. All English publications reporting the proportion of HNC specimens from SSA patients who tested positive for HPV and/or p16 were included. Study quality was assessed using the National Institutes of Health Quality Assessment Tool for Case Series Studies.

RESULTS In this systematic review of 31 studies and 3,850 patients, the overall p16 positivity was 13.6% (41 of 1,037 patients tested) with the highest proportion among oropharyngeal cancers (20.3%, 78 of 384 patients) and the overall HPV polymerase chain reaction positivity was 15.3% (542 of 3,548 samples tested) with the highest proportion among nasopharyngeal cancers (16.5%, 23 of 139 patients). Among the 369 HPV strains detected, the most common genotypes were HPV 16 (226 patients, 59.2%) and HPV 18 (78, 20.4%).

CONCLUSION HPV was found to be associated with a significant proportion of HNC in SSA. The genotypes reported suggest that the nine-valent vaccine and gender-neutral vaccination policies should be considered. Given that these studies may not accurately capture prevalence nor causation of HPV in HNC subsites, additional research is needed to provide a more thorough epidemiologic understanding of HPV-associated HNC in SSA, including risk factors and clinical outcomes.

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INTRODUCTION

Head and neck cancers (HNCs) are the seventh most commonly diagnosed malignancy globally.[1] Tobacco use and alcohol use are the major risk factors[1]; however, research over the past several decades has demonstrated strong links between human papillomavirus (HPV) and the development of HNCs, specifically in the oropharynx subsite.[2] Although overall rates of HNC are declining, the incidence of HPV-associated squamous cell carcinoma of the oropharyngeal subsite (OPSCC) has increased. In countries such as the United States, the incidence of HPV-associated HNC exceeds that of HPV-associated cervical cancer.[3-5] The survival advantage imparted by HPV association in HNC, specifically the oropharyngeal subsite, has resulted in biomarker-driven diagnosis and changes in the latest American Joint Committee on Cancer 8th edition staging system.[6] In addition, ongoing research is actively evaluating treatment de-escalation strategies among patients with HPV-associated HNC, with the goal of minimizing toxicity while preserving outcomes.[4,6,7]

Although the proportion of HPV-associated OPSCC is highest in North America at around 60%, regional variations exist; for instance, rates range from 10% in southern Europe to 50% in northern Europe.[8] To our knowledge, the proportion of HNCs in sub-Saharan Africa (SSA) associated with HPV is minimally characterized. This is a region of the world that holds the potential for higher proportions given that SSA has the greatest burden of HPV-driven malignancies, including cervical cancer, and the highest global prevalence of HIV,[8-20] which predisposes patients to increased rates of oral HPV infection and risk of developing head and neck squamous cell carcinomas.[21-26]

Characterizing HPV in HNCs is critical in SSA. Accurate data from the SSA region are needed to formulate health policies addressing the prevention, diagnosis, staging, and management of HNCs. Knowledge of the burden of HPV-associated HNC in SSA may influence whether regional ministries of health invest in developing in-country diagnostic capacity and incorporate HPV assessment into national treatment guidelines. The

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

In sub-Saharan Africa, what is the proportion of head and neck cancers with human papillomavirus (HPV) positivity?

Knowledge Generated

Among 31 studies including 3,850 patients, HPV positivity in the head and neck was assessed most commonly using p16 immunohistochemistry and HPV polymerase chain reaction. The overall p16 positivity was 13.6% with the highest proportion among oropharyngeal cancers (20.3%), and the overall HPV polymerase chain reaction positivity was 15.3% with the highest proportion among nasopharyngeal cancers (16.5%). The areas in which studies lacked in quality were clearly characterized patient populations, reporting of patients who presented consecutively, and detailed results.

Relevance

A portion of head and neck cancers in sub-Saharan African countries test positive for HPV, but additional research is needed to confirm these estimates, assess for risk factors, and characterize clinical outcomes.

improved prognosis of HPV-associated OPSCC may also change prioritization of limited oncologic resources including radiotherapy.[27-30] Finally, identification of a high burden of HPV-associated HNCs could lend support for expanding population-based HPV vaccination strategies.

Assessment of the proportion of HNCs associated with HPV in SSA is an important next step in building capacity for prevention and treatment of HPV-associated HNC in this setting. To address this knowledge gap, we performed a systematic review to report on the proportion of HPV-associated HNCs in SSA. Secondary outcomes of this study were HPV detection methods, the distribution of HPV positivity across head and neck anatomic subsites, and proportion of HPV genotypes. Although current guidelines recommend limiting p16 and HPV testing primarily to oropharyngeal squamous cell carcinomas,[4,31] this study includes all HNC subsites given early studies reporting HPV association in other subsites and tumor types[32-35] and to broadly capture studies within this systematic review.

MATERIALS AND METHODS

Study Design

This study was registered with the international prospective register of systematic reviews (PROSPERO, registration No. CRD42021252389) and was conducted according to Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines.[36]

Eligibility Criteria

This systematic review included all cohort, randomized controlled trials, case series, and case-control studies pertaining to HNC, HPV, and SSA. Abstracts from conferences were included if they contained adequate data for inclusion in the analysis. Specifically, studies were required to (1) involve patients with HNC, (2) pertain to patients from SSA, (3) describe HPV in the included study population, (4) report primary data, and (5) not only focus on one or only low-risk HPV subtypes. Head and neck pathologies in addition to squamous cell carcinoma were included given the hypothesized heterogeneity of studies. All publications in English until the date of the search were included.

The primary outcome was the proportion of HPV-associated HNCs reported in SSA. Secondary outcomes included methods used to detect HPV association in HNC, proportion of HNCs with HPV by subsite, and HPV genotypes present in HNCs in SSA.

Of note, the recommended clinical approach to testing for HPV involves p16 immunohistochemistry (IHC) given its high sensitivity and cost-effectiveness with additional testing for high-risk HPV genotypes performed at the discretion of the pathologist.[31,37] Additional testing may include HPV polymerase chain reaction (PCR) or HPV in situ hybridization (ISH). The association between p16 status and HPV is strongest for oropharyngeal cancers in comparison with other subsites.[31]

Data Sources and Search Strategy

The literature search was performed using MeSH terms related to HNC, HPV, and SSA with support from a librarian trained in literature searches. SSA countries were defined by the World Bank.[38] Reference lists of pertinent review articles and original research papers identified were also manually screened to identify additional relevant citations (see Appendix Fig A1 and Table A1-A3 for the full search strategy). The electronic databases searched as primary sources included PubMed, EMBASE, Web of Science, and African Index Medicus. Google Scholar and African Journals Online were also searched as secondary sources for any additional, relevant citations. The searches were initially performed on May 6, 2021, and an interval search was performed on May 11, 2022.

Study Selection and Data Collection

Citations identified from the search were uploaded into EndNote. Duplicates were removed. The resultant set of citations was uploaded into Rayyan, a systematic review reference classification platform. The title and abstracts of citations were screened for eligibility by three authors (SO,

LM, and MJX). For citations that reported on the same study population, the most recent citation was included. Data were abstracted by two authors (SO and MJX) in a standardized data collection form. Any discrepancies were adjudicated and reconciled between the two authors. Abstracted data included study characteristics, study population, p16 or HPV testing strategy, proportion of p16 or HPV positivity among HNC subsites, and HPV genotypes detected if relevant.

Quality Assessment

Study quality was assessed using the National Institutes of Health (NIH) Quality Assessment Tool for Case Series Studies by two authors (SO and MJX).[39] Discrepancies were reconciled. We defined scores of 1-5 as poor quality, 6-7 as fair, and 8-9 as good.

RESULTS

Study Selection

A total of 386 records were identified, of which 31 studies from 12 countries were included (Fig 1). Eight studies were from Sudan, six were from South Africa, four were from Ghana, three were from Uganda, three were from Nigeria, two were from Senegal, and one each was from Kenya, Cameroon, Central African Republic, Burkina Faso, Malawi, and Mozambique (Data Supplement). One study included study populations from both Nigeria and Senegal. Five papers were of prospective studies,[13,14,19,40,41] one paper did not report whether samples were collected prospectively or retrospectively,[42] and the remaining studies were retrospective.

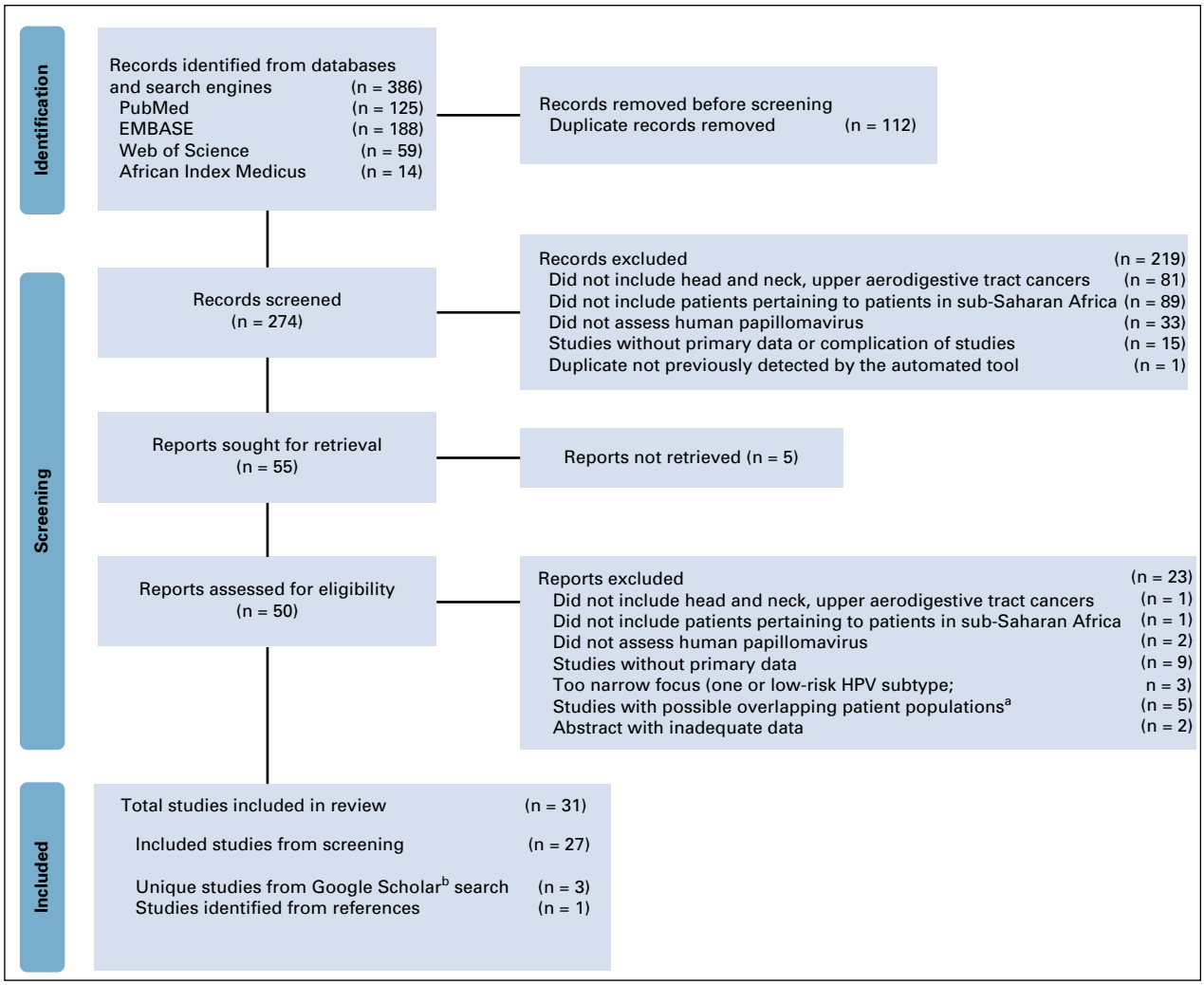

FIG 1. Preferred reporting items for systematic review and meta-analysis flow diagram for study selection and screening process (identification of studies via databases and registers). [a]Studies with possible overlapping patient populations were the ones in which there were studies from the same country, from the same lead author, and from the similar study period and where there was the possibility of overlapping patient cohorts. In these cases, the more recently published paper was included in the analysis. [b]Given differences in the Google Scholar search engine, a search was performed at the completion of the database.

HPV Testing

Of the 31 studies included (Table 1), seven tested by both p16 IHC and HPV PCR,[8,13-15,17,43] one study used HPV PCR and HPV ISH,[44] four studies used p16 IHC only,[18,19,40,45] and the remaining 19 studies used HPV PCR only. Among the seven studies that tested by both p16 IHC and PCR, four studies tested the whole patient population,[13,15,17,46] one study tested p16 only on the samples that were reported as HPV-positive by PCR,[8] and two studies tested by HPV only on the samples that tested positive by p16 IHC.[14,43] For the study that used both HPV PCR and HPV ISH, the ISH was only tested on the samples that were positive by HPV PCR.[44]

HPV Association

A total of 3,850 cases of HNCs were collectively reported in the literature. Of these, the following subsites were represented (in decreasing frequency): oral cavity (n = 1,398, 36.3%), larynx (n = 690, 17.9%), oropharynx (n = 570, 14.8%), nasopharynx (n = 145, 3.8%), sinonasal (n = 68, 1.8%), and hypopharynx (n = 47, 1.2%). Six studies included pathologic diagnoses other than squamous cell carcinoma,[14,45,47-50] and one study reported the pathologic diagnoses of samples that tested positive for HPV but not the overall cohort.[51]

TABLE 1. Aggregate p16 and HPV Positivities

No. of Studies	No.
Total	31
With p16 testing only	4
With HPV testing only	20
With both p16 and HPV testing	7

No. of Patients by Subsite	No.
Total	3,850
Oral cavity	1,398
Oropharynx	570
Nasopharynx	145
Larynx	690
Hypopharynx	47
Sinonasal	68

p16 Testing	Total Patients Tested (No.)	Positivity (No.)	Positivity (%)
All patients	1,037	141	13.6
Oral cavity	154	18	11.7
Oropharynx	384	78	20.3
Nasopharynx	9	1	11.1
Larynx	251	21	8.4
Hypopharynx	18	3	16.7
Sinonasal	6	0	0.0

HPV Testing	Total Patients Tested (No.)	Positivity (No.)	Positivity (%)
All patients	3,548	542	15.3
Oral cavity	1,372	134	9.8
Oropharynx	557	84	15.1
Nasopharynx	139	23	16.5
Larynx	655	55	8.4
Hypopharynx	39	2	5.1
Sinonasal	62	6	9.7

Abbreviation: HPV, human papillomavirus.

p16 IHC

Among patients, 1,037 underwent IHC staining for p16 (Table 1) with an overall p16 positivity rate of 13.6% (n = 105). The highest proportion was noted in oropharyngeal (20.3%, 78 of 384 patients), hypopharyngeal (16.7%, 3 of 18 patients), and oral cavity cancers (11.7%, 18 of 154 patients). When we assessed the 20 studies that only include head and neck squamous cell carcinomas of the upper aerodigestive tract,[8,13,15-19,40-44,46,52-58] the proportion of specimens that were positive for p16 IHC (Data Supplement) was similar to that when assessing all the studies (Table 1).

HPV ISH

To our knowledge, the study by Boy et al (2006)[44] was the only study to test for HPV with HPV ISH. In their retrospective study of patients from South Africa, they tested ISH on samples that tested positive by HPV PCR. Among those seven samples, none were positive on HPV ISH (Table 2). When the 20 studies that only include head and neck squamous cell carcinomas of the upper aerodigestive tract were assessed,[8,13,15-19,40-44,46,52-58] the proportion of specimens that were positive for HPV (Data Supplement) was similar to that when assessing all the studies (Table 1).

HPV Genotypes

For HPV testing, 3,548 patients were tested by HPV PCR (Table 1) with an overall positivity of 15.3% (n = 542). The nasopharyngeal subsite had the highest proportion of HPV positivity (16.5%, 23 of 139 patients), followed by oropharynx (15.1%, 84 of 557 patients) and oral cavity (9.8%, 134 of 1,372 patients). Specific HPV genotypes were reported for 382 strains detected across all subsites (Table 3). The most commonly reported was HPV 16 (226, 59.2%), HPV 18 (78, 20.4%), and HPV 56 (19, 5.0%). Among the three papers that reported on patients with oropharyngeal cancer and HPV genotypes,[13,46,59] the most common were HPV 16 (17 of 27, 63.0%) and HPV 6, 13, and 52 (2 of 27, 7.4% each).

Risk Factors

Seven studies reported tobacco use in patients, which ranged from 20.0% to 66.8%.[18,19,40,41,46,48,57] Alcohol use was reported by five studies, ranging from 8.0% to 85.0%.[19,40,41,46,48] Sexual history was reported in two studies.[40,41]

The proportion of HIV-positive patients ranged from 4.9% to 27.1% among four studies.[19,40,41,48] There were two papers that reported HIV and HPV coinfection among patients with head and neck squamous cell carcinoma.[18,40] In the study

TABLE 2. Study Details

First Author (Publication Year)	Country	Study Period	Histology (No.)	Subsite (No.)								p16 Positivity, Subsite (No.)								HPV Positivity, Subsite (No.)							
				All	OC	OP	NP	L	HP	SN	Others	All	OC	OP	NP	L	HP	SN	Others	All	OC	OP	NP	L	HP	SN	Others
Studies with both p16 and HPV testing																											
Dapaah (2022)[46]	South Africa	2007-2017	SCC (266)	266		266						36		36						13		13					
Rettig (2019)[43]	Cameroon	2011-2017	SCC (7)	7	0	7		0				2		2						2		2					
Sekee (2018)[13]	South Africa	2014-2017	SCC (112)	112		20	3	79	10			19		5	1	11	2			7		1	1	4	1		
Castellsagué (2016)[8]	Nigeria, Senegal	1990-2012	SCC (131)	131	58			73				0				0				6	2			4			
Blumberg (2015)[15]	Mozambique	2005-2013	SCC (51)	51	29	22						2	2	0						0	0	0					
Paquette[a] (2013)[17]	South Africa	2005-2010	SCC (51)	51		51						26		26						48		48					
Ndiaye (2013)[14]	Senegal	2002-2010	SCC (112)	117	41	5		64			Pharynx 7	0	0			0				4	1			3			
			Adenocarcinoma 1																								
			Others 4																								
Studies with p16 testing																											
Kabagenyi (2020)[40]	Uganda	2018-2019	SCC (59)	59	17	13		22	7			12	5	4		2	1										
Nabukenya (2018)[19]	Uganda	2016-2016	SCC (51)	51	9			9		6	Pharynx 19	6		5		1											
											UP 8																
Faggons (2017)[18]	Malawi	2010-2014	SCC (42)	42			6	4	1		OC and OP 23	7			0	2	0		OC and OP 5								
											UP 8								UP 0								
Ahmed (2012)[45]	Sudan	Not reported	SCC (144)	150								31	11			5			Pharyngeal 4								
			Adenocarcinoma 6																Esophageal 7								
																			Others 4								
Studies with HPV testing																											
Mohamed (2021)[47]	Sudan	2018-2019	SCC (132)	150	26	6	30	12			Esophageal SCC 40									26	4	0	0	6			Esophageal 14
			Salivary 18								Conjunctival SCC 18																Adenoid cystic salivary 2
											Salivary 18																
Akhiwu (2021)[48]	Nigeria	2017-2019	SCC (31)	41	10	21	4				Palate 6 (unclear if hard or soft palate)									7							
			Kaposi sarcoma 1																								
			Nasopharyngeal carcinoma 1																								
			NHL 2																								
			Adenoid cystic carcinoma 2																								
			Melanoma 1 Ameloblastic carcinoma 3																								

(Continued on following page)

TABLE 2. Study Details (Continued)

First Author (Publication Year)	Country	Study Period	Histology (No.)	Subsite (No.)								p16 Positivity, Subsite (No.)								HPV Positivity, Subsite (No.)							
				All	OC	OP	NP	L	HP	SN	Others	All	OC	OP	NP	L	HP	SN	Others	All	OC	OP	NP	L	HP	SN	Others
Bulane (2020)[59]	South Africa	2004-2014	SCC (780)	780	329	120	26	259	17	25	Eye 2									57	20	13	1	18	1	4	0
											Trachea 1																
											Lymph node 1																
Aswani (2019)[41]	Kenya	2015-2017	SCC (160)	160	14	8	62	47	11	18	0									12	2	0	7	1	0	2	
Kofi (2019)[49]	Central African Republic	2009-2017	SCC (129)	135	45	19	9	37			Unspecified pharyngeal 25									1		1					
			Adenocarcinomas 6																								
Ilboudo (2019)[50]	Burkina Faso	2007-2017	Carcinoma 97	128							Ear 3									20							
			Lymphoma 14																								
			Melanoma 4																								
			Sarcoma 7																								
			Cylindromas 6																								
Aboagye (2019)[20]	Ghana	2007-2016	SCC (100)	100	23	12	5	26	1	18	Salivary 4									18	5	6	0	7	0	0	0
											Unknown 11																
Biira (2019)[52]	Uganda	2010-2015	SCC (200)	200																174							
Dawson (2018)[53]	Ghana	2006-2013	SCC (88)	88	88															3	3						
Asante (2017)[54]	Ghana	2006-2012	SCC (72)	72																14			14				
Oga (2016)[16]	Nigeria	1990-2011	SCC (7)	7				6		1										0				0		0	
Jalouli (2015)[42]	Sudan	Not reported	SCC (57)	57	57															18	18						
Kaba (2014)[12]	Ghana	2007-2009	SCC (78)	78	29			33			Pharynx 11									15	4			8			Pharynx 2
											Parotid 5																Parotid 1
Babiker (2013)[51]	Sudan	Not reported	Unclear	100	100															8							
Husain (2012)[55]	Sudan	2005-2009	SCC (95)	95																10							
Ginawi (2012)[56]	Sudan	2009-2010	SCC (50)	50	50															10	10						
Ahmed (2012)[45]	Sudan	Not reported	SCC (150)	150	51			19			Pharynx 17									6	2			4			
											Esophagus 53																
											Others 10																
Jalouli (2010)[57]	Sudan	Not reported	SCC (217)	217	217															54	54						
Boy (2006)[44,b]	South Africa	1998-2003	SCC (59)	59	59															7	7						
Van Rensburg (1996)[58]	South Africa	Not reported	SCC (146)	146	146															2	2						

Abbreviations: HP, hypopharynx; HPV, human papillomavirus; L, larynx; NHL, non-Hodgkin lymphoma; NP, nasopharynx; OC, oral cavity; OP, oropharynx; SCC, squamous cell carcinoma; SN, sinonasal.

[a]51 samples from 41 patients.

[b]Study also tested HPV polymerase chain reaction–positive samples by in situ hybridization, in which none of the seven samples were positive.

TABLE 3. HPV Genotypes Detected Details

	HPV Genotypes													
HPV Strains and Percentage	**2**	**6**	**11**	**13**	**16**	**18**	**31**	**33**	**35**	**39**	**45**	**52**	**56**	**59**
Total No. of HPV strains	1	10	6	2	226	78	6	14	3	1	7	8	19	1
Percentage of total	0.3	2.6	1.6	0.5	59.2	20.4	1.6	3.7	0.8	0.3	1.8	2.1	5.0	0.3
	HPV Genotypes													
Author (publication year)	**2**	**6**	**11**	**13**	**16**	**18**	**31**	**33**	**35**	**39**	**45**	**52**	**56**	**59**
Dapaah et al (2022)[46]					10	1	1					1		
Mohamed et al (2021)[47]					26									
Akhiwu et al (2021)[48]					4			3	1			1		
Bulane et al (2020)[59]	1	10	3	2	26	2	2	3	1		3	3		1
Aswani et al (2019)[41]								1				1	10	
Kofi et al (2019)[49]					1									
Ilboudo et al (2019)[50]					2	2		6		1	1	1	9	
Aboagye et al (2019)[20]					18	1								
Biira et al (2019)[52]					92	41								
Dawson et al (2018)[53]					1	1						1		
Sekee et al (2018)[13]			2		2	1	1				1			
Asante et al (2017)[54]						13	1							
Castellsagué et al (2016)[8]					2									
Kaba et al (2014)[12]					13	3								
Ndiaye et al (2013)[14]					1				1		2			
Babiker et al (2013)[51]					5	1	1	1						
Husain et al (2012)[55]					16									
Ginawi et al (2012)[56]					6	5								
Boy et al (2006)[44]						7								
Van Rensburg et al (1996)[58]			1		1									

Abbreviation: HPV, human papillomavirus.

by Kabagenyi et al,[40] 6.8% of patients (4 of 59 patients) were HIV-positive and had tumors that were p16-positive. Similarly, in the study by Faggons et al (2017),[18] the proportion of coinfection was 5.9% (1 of 17 patients). Anatomic subsites were combined in these results, and no studies reported clinical outcomes of HIV- and HPV-coinfected patients.

Quality Assessment and Risk of Bias Within Studies

On the basis of the NIH Quality Assessment Tool for Case Series Studies, 19 studies were rated as good quality and 12 studies were deemed fair (Table 4). The areas in which the most studies lacked in quality were clearly characterized patient populations, reporting of patients who presented consecutively, and well-described results.

DISCUSSION

Although recognition of HPV-associated OPSCC has changed treatment paradigms in high-resource health systems,[6,7] less is known about the proportions of HNCs with HPV association in SSA. Meanwhile, the greatest burden of HPV-driven malignancies intersects with the highest prevalence of HIV infection in this setting.[23,60] To our knowledge, this is the first systematic review assessing associations between HPV and malignancies in head and neck subsites in SSA. Two international studies, one meta-analysis and one internationally coordinated analysis of head and neck carcinomas, previously reported global proportions of HPV-associated HNSCC to be 31.5% and 12.2%.[8,10] These studies, however, included no data on oropharyngeal cancers from SSA and limited data from other head and neck subsites of patients from SSA. Our systematic review noted an overall HPV association in 13.6% of patients on the basis of p16 testing and 15.3% on the basis of HPV testing. The slightly higher rate noted with HPV testing may be due to incidental infection of HPV.

In terms of HPV association in the oropharynx, studies have highlighted regional variations although data from SSA countries are sparse. In a systematic review by Carlander et al[61] (2021), 31 studies involving 49,564 patients with OPSCC were assessed and the worldwide positivity ranged from 0% to 85%, with wide geographic variation. The highest rates were found in Northern European countries,

TABLE 4. Quality of Studies Using the National Institutes of Health Quality Assessment Tool for Case Series Studies

Author (publication year)	1. Was the Study Question or Objective Clearly Stated?	2. Was the Study Population Clearly and Fully Described, Including a Case Definition?	3. Were the Cases Consecutive?	4. Were the Participants Comparable?	5. Was the Intervention Clearly Described?	6. Were the Outcome Measures Clearly Defined, Valid, Reliable, and Implemented Consistently Across All Study Participants?	7. Was the Length of Follow-Up Adequate?	8. Were the Statistical Methods Well-Described?	9. Were the Results Well-Described?	Quality Rating
Dapaah et al (2022)[46]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Mohamed et al (2021)[47]	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	Good
Akhiwu et al (2021)[48]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Fair
Kabagenyi et al (2020)[40]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Good
Bulane et al (2020)[59]	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	Yes	Good
Aswani et al (2019)[41]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Rettig et al (2019)[43]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Kofi et al (2019)[49]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Good
Ilboudo et al (2019)[50]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Fair
Aboagye et al (2019)[20]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Biira et al (2019)[52]	Yes	No	NR	Yes	Yes	Yes	Yes	Yes	No	Fair
Dawson et al (2018)[53]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Nabukenya et al (2018)[19]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Sekee et al (2018)[13]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Faggons et al (2017)[18]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Good
Asante et al (2017)[54]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Oga et al (2016)[16]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Fair
Castellsagué et al (2016)[8]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Good
Jalouli et al (2015)[42]	Yes	No	NR	No	Yes	Yes	Yes	Yes	Yes	Fair
Blumberg et al (2015)[15]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Kaba et al (2014)[12]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Paquette et al (2013)[17]	Yes	No	NR	Yes	Yes	Yes	Yes	Yes	Yes	Fair
Ndiaye et al (2013)[14]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Babiker et al (2013)[51]	Yes	Yes	NR	Yes	Yes	Yes	Yes	Yes	No	Fair
Husain et al (2012)[55]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Fair
Ginawi et al (2012)[56]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Ahmed et al (2012)[45]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Fair
Ahmed et al (2012)[45]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Fair
Jalouli et al (2010)[57]	Yes	No	NR	Yes	Yes	Yes	Yes	Yes	Yes	Fair
Boy et al (2006)[44]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Van Rensburg et al (1996)[58]	Yes	No	NR	Yes	Yes	Yes	Yes	Yes	Yes	Fair

Abbreviation: NR, not reported.

the United States, Lebanon, China, and South Korea. Additional international studies have reported HPV-associated OPSCC to be 45.8% and 22.4%.[8,10] Our study found HPV association for OPSCC in 20.3% of patients on the basis of p16 testing and 15.1% of patients on the basis of HPV testing. Although these rates are among the lower ranges reported globally, Chaturvedi et al[62] (2013) noted that between 1988 and 2002, HPV-positive OPSCC tumors increased among younger males in developed countries. As more of the SSA country economies continue to develop, there is a potential for a surge in HPV-positive OPSCC to rates comparable with developed countries. In addition, these lower rates found in studies centered in SSA are in the context of limited testing for HPV association in many SSA nations. Indeed, Fagan et al[63] (2020) reported that 16 of 17 head and neck surgeons in SSA surveyed did not have routine access to p16 testing.

Interestingly, the proportion of nasopharyngeal cancers (NPC) with HPV positivity as tested by HPV PCR was the greatest among subsites at 16.5%. Globally, NPC is most prevalent in Asia and SSA and associated with the Epstein-Barr virus (EBV).[64] Stenmark et al[33] (2014) noted that patients with HPV-positive/EBV-negative NPCs have worse prognosis than patients who are HPV-negative/EBV-positive. Given the small sample size and heterogeneous nature of studies of this systematic review, more testing is needed to confirm the association and prognostication of HPV in NPC.

Currently, p16 IHC and/or HPV testing is not routinely recommended as part of guidelines for HNCs in SSA.[65,66] This is due to challenges related to reagent cost or supply and/or technical aspects of p16 and HPV testing.[67] However, our data highlight a need for HPV testing to be included as part of standard care practices. Certainly, knowledge of HPV positivity conveys important prognostic implications and could help inform treatment decisions. Given the heterogeneity of the existing studies, routine p16 and HPV testing of HNC would provide a more comprehensive understanding of the epidemiology of HPV-associated HNC and OPSCC in SSA. Without this information, which is incorporated into the latest tumor staging system, patients in SSA without access to p16 testing could be at a disadvantage because of not receiving prognostic information and limiting their treatment options with the risk of unnecessary toxcitiy.[63] Cost is a critical barrier to implementation of p16 testing; assessing cost and considering newer point-of-care testing could aid in increased adoption of HPV testing in SSA.[68] Furthermore, with active research into treatment de-escalation for patients with HPV-associated OPSCC, an understanding of the burden of HPV-associated HNC in SSA could lead to reprioritization and reallocation of limited resources for patients with HNC.

Finally, knowledge of the prevalence of subtypes is highly relevant to vaccination programming. Currently, the quadrivalent HPV vaccine covering genotypes 6, 11, 16, and 18 is available in SSA through Gavi, the Vaccine Alliance, for prevention of cervical cancer.[69] In the case of cervical cancer, studies have reported that high-risk subtypes including HPV 45 are more prevalent in SSA,[23] which may influence future adoption of the nine-valent vaccine that covers for HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58.[70] In this study, we found that HPV 16 is the most prevalent genotype detected in HNCs and oropharyngeal cancers. Among all subsites, HPV 18 and HPV 56 were the next most common, the latter of which is currently not covered by the nine-valent vaccine. These data highlight a need to re-evaluate population-based vaccine strategies, particularly given that the potential benefit may extend beyond cervical cancer and include meaningful reduction of the burden of HNC.

A major limitation of this systematic review is the heterogeneity of methodologies among the included studies, minimal data on risk factors, and limited staging and outcomes data. Only 7 of 31 studies tested for both p16 and HPV status. Currently, the standard for testing is to use p16 IHC first as a surrogate for HPV association in tumors involving the oropharynx with follow-up high-risk HPV genotyping used in select scenarios.[31] Given that HPV positivity in the absence of p16 positivity may indicate incidental HPV infection, the 20 studies that only tested using HPV PCR would require additional testing such as HPV ISH to confirm the HPV integration. These tests also require training and standardized interpretation, which may influence the results. Furthermore, only six studies reported patient risk factor data,[18,19,40,41,48,57] only two papers provided staging information,[19,41] and only one paper reported long-term clinical outcomes.[19] These variables are critically needed to understand the epidemiology of and context of HPV-associated HNC in SSA.

In conclusion, HPV-associated HNCs comprise a significant proportion of HNCs in SSA. The genotypes reported suggest that the nine-valent vaccine and gender-neutral vaccination policies should be re-evaluated. Given the growing burden of malignancy in SSA, increased research is needed to understand the epidemiology of HPV-associated HNCs, long-term clinical outcomes, and how these data influence treatment guidelines and vaccination policies.

AFFILIATIONS

[1]ENT, Kenyatta National Hospital, ENT Department, Nairobi, Kenya
[2]ENT, Kenyatta University Teaching, Research and Referral Hospital, Nairobi, Kenya
[3]Department of Oncology, Rwanda Military Hospital, Kigali, Rwanda
[4]Rwanda Cancer Relief, Kigali, Rwanda
[5]Department of Otorhinolaryngology, Muhimbili National Hospital, Dar es Salaam, Tanzania
[6]Department of Medicine, University of California San Francisco, San Francisco, CA
[7]Department of Medicine, Division of Hematology and Oncology, University of California, San Francisco, CA

[8]Department of Otolaryngology-Head and Neck Surgery, University of California San Francisco, San Francisco, CA
[9]Division of Otolaryngology, University of Cape Town, Cape Town, South Africa
[10]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY
[11]Department of Surgery, University of Nairobi, Nairobi, Kenya

CORRESPONDING AUTHOR

Samuel Okerosi, MBChB, MMed, ENT Department, Kenyatta National Hospital, 58914-00200, Nairobi, Kenya; email: snokerosi@gmail.com.

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AUTHOR CONTRIBUTIONS

Conception and design: All authors
Administrative support: Katherine Van Loon, Joyce Aswani
Collection and assembly of data: Samuel Okerosi, Lillian Wairimu Mokoh, Brandon Asuman Niyibizi, Aslam Nkya, Mary Jue Xu
Data analysis and interpretation: Samuel Okerosi, Fidel Rubagumya, Brandon Asuman Niyibizi, Aslam Nkya, Katherine Van Loon, Geoffrey Buckle, Stephen Bent, Johannes J. Fagan, Dianna Ng, Mary Jue Xu
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Samuel Okerosi
Travel, Accommodations, Expenses: Krishna Chemists

Patrick Ha
Consulting or Advisory Role: Rakuten Medical, Checkpoint Surgical, Privo Technologies
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APPENDIX

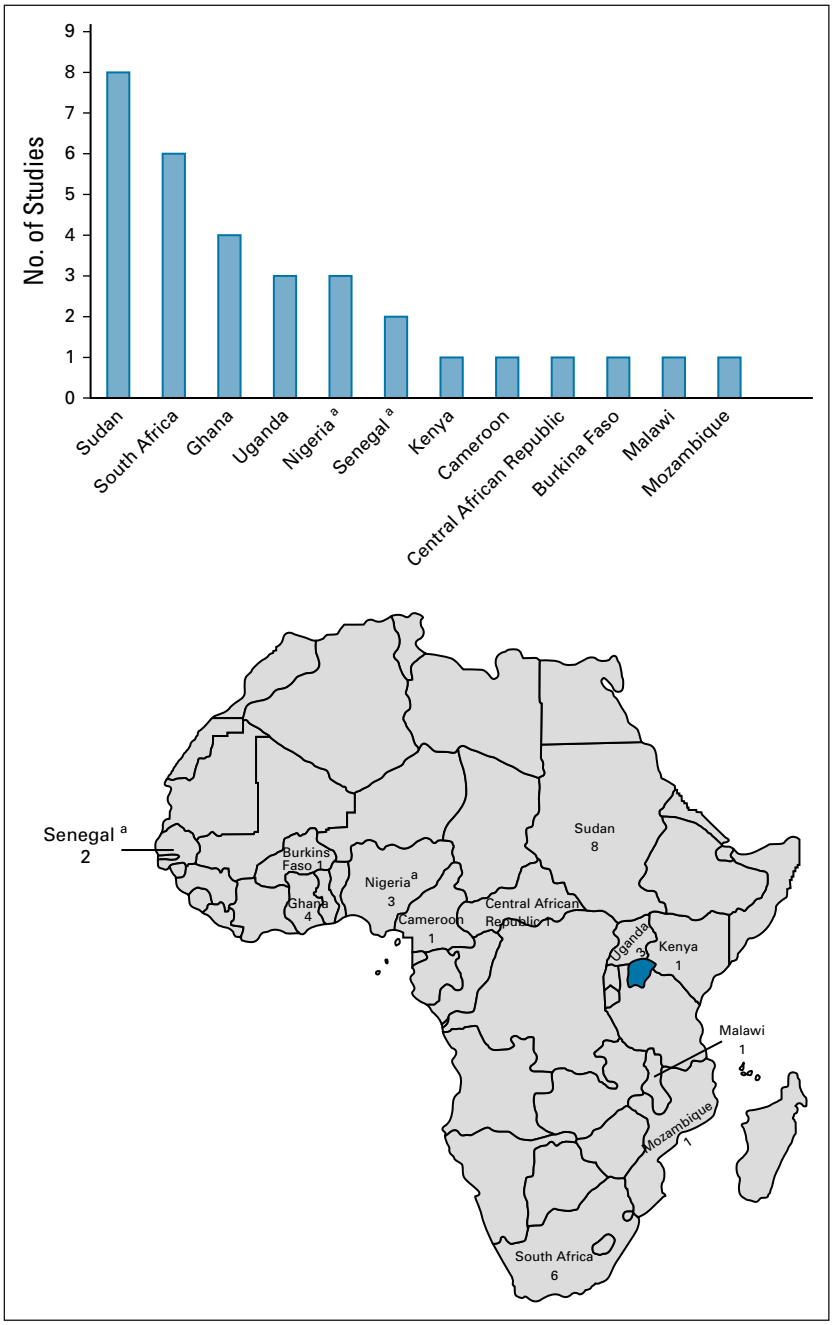

FIG A1. Number of studies per country. [a]One study included patients from both Nigeria and Senegal.

TABLE A1. Aggregate p16 and HPV Positivities for Studies Only Including Patients With Squamous Cell Carcinoma

No. of Studies	No.
Total	20
With p16 testing only	9
With HPV testing only	17
With both p16 and HPV testing	6

No. of Patients by Subsite	No.
Total	1,921
Oral cavity	744
Oropharynx	387
Nasopharynx	71
Larynx	240
Hypopharynx	29
Sinonasal	25

p16 Testing	Total Patients Tested (No.)	Positivity (No.)	Positivity (%)
All patients	770	110	14.3
Oral cavity	113	7	6.2
Oropharynx	379	78	20.6
Nasopharynx	9	1	11.1
Larynx	187	16	8.6
Hypopharynx	18	3	16.7
Sinonasal	6	0	0.0

HPV Testing	Total Patients Tested (No.)	Positivity (No.)	Positivity (%)
All patients	1,769	380	21.5
Oral cavity	718	98	13.6
Oropharynx	374	64	17.1
Nasopharynx	65	22	33.8
Larynx	205	9	4.4
Hypopharynx	21	1	4.8
Sinonasal	19	2	10.5

Abbreviation: HPV, human papillomavirus.

TABLE A2. Aggregate p16 and HPV Positivities for Studies With the Study Period From 2015 Onward

No. of Studies	No.
Total	5
With p16 testing only	2
With HPV testing only	3
With both p16 and HPV testing	0

No. of Patients by Subsite	No.
Total	461
Oral cavity	76
Oropharynx	48
Nasopharynx	96
Larynx	90
Hypopharynx	18
Sinonasal	24

p16 Testing	Total Patients Tested (No.)	Positivity (No.)	Positivity (%)
All patients	110	18	16.4
Oral cavity	26	5	19.2
Oropharynx	13	9	69.2
Nasopharynx	0	0	0.0
Larynx	31	3	9.7
Hypopharynx	7	1	14.3
Sinonasal	6	0	0.0

HPV Testing	Total Patients Tested (No.)	Positivity (No.)	Positivity (%)
All patients	351	45	12.8
Oral cavity	50	6	12.0
Oropharynx	35	0	0.0
Nasopharynx	96	7	7.3
Larynx	59	7	11.9
Hypopharynx	11	0	0.0
Sinonasal	18	2	11.1

Abbreviation: HPV, human papillomavirus.

TABLE A3. Aggregate p16 and HPV Positivities for Studies With Study Periods Before 2015

No. of Studies	No.
Total	20
With p16 testing only	8
With HPV testing only	19
With both p16 and HPV testing	7

No. of Patients by Subsite	No.
Total	2,569
Oral cavity	751
Oropharynx	522
Nasopharynx	49
Larynx	577
Hypopharynx	28
Sinonasal	44

p16 Testing	Total Patients Tested (No.)	Positivity (No.)	Positivity (%)
All patients	777	92	11.8
Oral cavity	128	2	1.6
Oropharynx	371	69	18.6
Nasopharynx	9	1	11.1
Larynx	220	13	5.9
Hypopharynx	11	2	18.2
Sinonasal	0	0	0.0

HPV Testing	Total Patients Tested (No.)	Positivity (No.)	Positivity (%)
All patients	2,527	409	16.2
Oral cavity	751	52	6.9
Oropharynx	522	84	16.1
Nasopharynx	43	16	37.2
Larynx	577	44	7.6
Hypopharynx	28	2	7.1
Sinonasal	44	4	9.1

Abbreviation: HPV, human papillomavirus.