Review: Head and neck squamous cell carcinoma in sub-Saharan Africa

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Abstract

Aim

Review the literature from 1990 to 2013 to determine known anatomic sites, risk factors, treatments, and outcomes of head and neck squamous cell carcinoma (HNSCC) in sub-Saharan Africa.

Methods

Using a systematic search strategy, literature pertaining to HNSCC in sub-Saharan Africa was reviewed and patient demographics, anatomic sites, histology, stage, treatment, and outcomes were abstracted. The contributions of human immunodeficiency virus (HIV), human papillomavirus (HPV) and behavioural risk factors to HNSCC in the region were assessed.

Results

Of the 342 papers identified, 46 were utilized for review, including 8611 patients. In sub-Saharan Africa, the oropharyngeal/oral cavity was found to be the most common site, with 7750 cases (90% of all cases). Few papers distinguished oropharyngeal from oral cavity, making identification of possible HPV-associated oropharyngeal squamous cell carcinoma (SCC) difficult. SCC of the nasopharynx, nasal cavity, or paranasal sinuses was identified in 410 patients (4.8% of all cases). Laryngeal SCC was found in 385 patients (4.5% of all cases), and only 66 patients (0.8% of all cases) with hypopharyngeal SCC were identified. In 862 patients with data available, 43% used tobacco and 42% used alcohol, and reported use varied widely and was more common in laryngeal SCC than that of the oropharyngeal/oral cavity. Toombak and kola nut use was reported to be higher in patients with HNSCC. Several papers reported HIV-positive patients with HNSCC, but it was not possible to determine HNSCC prevalence in HIV-positive compared to negative patients. Reports of treatment and outcomes were rare.

Conclusions

The oropharyngeal/oral cavity was by far the most commonly reported site of HNSCC reported in sub-Saharan Africa. The roles of risk factors in HNSCC incidence in sub-Saharan Africa were difficult to delineate from the available studies, but a majority of patients did not use tobacco and alcohol.

Introduction

Sub-Saharan Africa is experiencing a rapidly increasing burden of cancer-related morbidity and mortality. While annual deaths in the region resulting from human immunodeficiency virus (HIV),[1] tuberculosis,[2] and malaria[3] are steadily declining, cancer deaths are projected to increase by 85% between 2008 and 2030.[3] Moreover, these projections assume static age-specific incidence rates and are based solely on projected population growth and aging. Population-based cancer registries, however, demonstrate increasing cancer incidence, likely resulting from HIV and westernization of lifestyles.[5,6,7] This suggests future cancer burden in the region may be significantly underestimated.

Earlier cancer detection via screening, insights into tumour biology and pathogenesis, as well as improved treatments and supportive care, have contributed to increasing cancer survivorship in high-income countries. However, cancer patients in sub-Saharan Africa have largely not benefited from these advances and outcomes remain poor because of severely limited resources for diagnosis and treatment, as well as possible differences in the aetiology and pathogenesis of cancer in this region.[8]

The sites of lip, oral cavity, nasopharynx, other pharynx, and larynx, collectively, comprised the sixth most common cancer in sub-Saharan Africa, with 18,099 reported cases in 2008.[9] Upper aerodigestive tract cancers are staged according to the American Joint Commission on Cancer (AJCC) staging manual, by site and sub-site, based on the complex anatomy and physiology of the head and neck region. The aerodigestive anatomic sites delineated by AJCC are sinonasal, nasopharynx, oropharynx, oral cavity, hypopharynx, and larynx. Across all head and neck sites, the most common histology is squamous cell carcinoma (SCC).[10] Head and neck anatomy, as it pertains to staging cancers, requires specific training. There are only a limited number of head and neck surgeons in sub-Saharan Africa, and this review highlights the need for better anatomic understanding and staging.

For head and neck squamous cell carcinoma (HNSCC) patients, tobacco and alcohol use have historically been the most common risk factors.[11] Although tobacco use remains uncommon in most of sub-Saharan Africa, tobacco companies are aggressively marketing cigarettes throughout the region, targeting youth in particular.[12] Over the past several decades, tobacco use has increased by nearly 50% in low-and-middle-income countries (LMIC), generally, while simultaneously declining in high-income countries.[13]

While tobacco use has decreased in high-income countries, HNSCC burden has not significantly declined, partly explained by the emergence of human papillomavirus (HPV) as an aetiologic agent of oropharynx (OP) squamous cell carcinoma.[14] In sub-Saharan Africa, infectious agents play a directly causative role in one-third of cancers,[15] and HPV is the aetiologic agent of cervical cancer, the most common cancer in the region.[6] However, the contribution of HPV to HNSCC in sub-Saharan Africa is not well described, particularly in settings where HIV is highly prevalent, and where HIV-infected individuals may have increased acquisition and persistence of oncogenic HPV strains at multiple anatomic sites.[16,17]

This is a comprehensive review of the literature pertaining to HNSCC in sub-Saharan Africa. We systematically reviewed the regional literature with respect to HNSCC, including summarizing all available data regarding patient demographics, behavioural risk factors, HIV, HPV, anatomic site, histology, stage, treatment, and outcomes. Limitations of the existing literature are highlighted, and areas for future research are proposed.

Methods

Search strategy

PubMed was searched for all English- or French-language papers identified using the MeSH terms "head and neck cancer", "squamous cell carcinoma", and "Africa", and limiting results to studies of human subjects. Additional papers were identified from a bibliographic search of the studies identified. Since the HIV epidemic has had major

http://dx.doi.org/10.4314/mmj.v27i3.2

effects on the pattern of malignancies in the region, 1990 was chosen as the starting year for this review. Papers from North Africa were excluded, as were series reporting on fewer than five patients. For duplicative papers reporting on the same groups of patients, we included the publication describing the largest series of HNSCC patients specifically. Many studies reported on several pathologies of oral, nasal, or laryngeal neoplasms, from which data regarding HNSCC were extracted. Given that sinonasal undifferentiated carcinoma (SNUC) and nasopharyngeal carcinoma (NPC) include SCC histologies, these subtypes were included.

Data analysis

A standardized abstraction tool was developed to extract data from papers identified and to characterize studies based on inclusion and exclusion criteria. Data were abstracted from each paper with respect to primary tumour site or subsite, disease stage, patient sex, behavioural risk factors, patient HIV status, patient HPV status, treatment, complications, and outcomes. We described male-to-female ratios, substance use, HIV prevalence, HPV frequency, and tumour stage by summing the numbers of patients across all studies, stratifying by anatomic site. Data were omitted if HNSCC patients could not be extrapolated from aggregate tumour data.

Anatomic classification

Anatomic sites were not uniformly reported or defined in the studies reviewed. For our analysis, carcinomas were grouped as oral cavity (OC) and oropharynx (OP), nasal cavity (NC), nasopharynx (NP), paranasal sinuses, larynx, and hypopharynx (HP). The AJCC cancer staging manual was used to delineate these sites, as defined below.[18] For papers including multiple anatomic sites, we analyzed carcinomas separately by anatomic site.

OC is defined as mucosal lip, buccal mucosa, alveolar ridge (gums or gingiva), retromolar trigone, hard palate, floor of mouth, and anterior two-thirds of the tongue. OP includes the inferior surface of the soft palate, tonsillar beds, tongue base, and lateral and posterior pharyngeal walls, from the level of the soft palate to the tip of the epiglottis. The dividing line between OC and OP is the junction of the hard and soft palate and the lingual circumvallate papillae. It was frequently not possible to distinguish OC from OP based on available data, therefore these two anatomic sites were analyzed in aggregate. NC is anatomically defined as extending from the nares to the choanae, including the turbinates. NP was defined as extending posteriorly from the choanae, including the lateral and posterior pharyngeal walls, down to the free edge of the soft palate. The paranasal sinuses include the maxillary, ethmoid, frontal, and sphenoid sinuses. The larynx subsites are the supraglottis, glottis, and subglottis. The supraglottis subsites are epiglottis, aryepiglottic folds, arytenoids and false vocal cords. The glottis includes the true vocal cords, and anterior and posterior commissures. A transglottic cancer extends through all three divisions of the larynx. HP is defined as extending inferiorly from the level of the epiglottis to the oesophageal introitus and includes three subsites: the postcricoid region, the right and left pyriform sinuses, and the posterior pharyngeal wall.[18]

Results

The initial PubMed search returned 330 papers, with an additional 12 papers identified using references of papers from the initial search. Of these 342 total papers, 60 included HNSCC in Africa and were published after 1990. Fourteen articles were excluded, leaving 46 studies in this review. Two excluded studies described regions other than sub-Saharan Africa.[19,20] Other excluded studies were a series of patients with specifically late presentations of benign and malignant orofacial tumours,[21] virological studies of pathology specimens without accompanying clinical data,[22-24] and studies exclusively examining SCC metastases to salivary glands.[25,26] We attempted to extrapolate HNSCC data from papers reporting SCC at multiple sites, but several papers were excluded because they only reported aggregate data, such that we could not distinguish HNSCC from the larger SCC group. Five papers that duplicated patients from other studies were excluded.[27-31] Overall, 8611 patients were included in the review.

Demographics, anatomic sites, and histology

Twenty-nine papers were identified that included SCC of the OC/OP, with a total of 7750 patients (90% of all cases identified, Table 1). The mean or median age of patients ranged from 37 years in Kenya[39] to 58 years in Ghana,[47] but there were insufficient patient-level data to report an aggregate mean or median age across all studies. The mean age of 37 was reported from a study of exclusively HIV-infected HNSCC patients in Kenya.[39] The youngest mean age in a generalized OC/OP SCC population was 46 years from Congo.[32] Male-to-female ratios ranged from 0.5:1 in Congo[32] to 4:1 in South Africa.[44] Overall, there were 2.3 males per female with OC/OP SCC across all studies. The most common OC/OP subsites were the mandibular or maxillary alveolar ridge in 1007 cases (13%), followed by the tongue in 773 (10%). In 57% of cases the site was not specified. OP sites were specified in only 171 cases (2%). The degree of differentiation was described in 835 cases (11%). Well-differentiated, moderately differentiated, and poorly differentiated carcinomas comprised 42%, 37%, and 25%, respectively.

Ten studies, including 410 patients, reported data from patients with cancer of the nasopharynx (NP), nasal cavity (NC), or paranasal sinuses (4.8% of all cases, Table 2). Few of these studies reported age and gender, but mean or median ages ranged from 4962 to 51 years,[63] and male-to-female ratios ranged from 1.7:163 to 2.3:1.61 Among SCCs of the NC, NP, and paranasal sinuses, the maxillary sinus was the most common subsite, comprising 53% of all tumours. Among NC, NP, and paranasal sinus SCCs, 71% were well-differentiated. Of the 73 NP carcinomas that were described with a WHO histologic classification, 26 (46%) were class I (keratinizing, differentiated SCC), while 47 (64%) were class II or III (undifferentiated carcinomas).

Ten studies discussed laryngeal carcinoma, including 385 patients (4.5% of all cases, Table 3). Mean or median ages ranged from 49 years in Cameroon[68] to 70 years in Nigeria.[69] Male-to-female ratios ranged from 6:1 in South Africa[45] and Nigeria[70] to 28:1 in Zimbabwe,[67] and the average ratio was 13:1. Lesion subsite was available for 240 patients and, of these, 62% were glottic. Two studies of laryngeal SCC noted the degree of histologic differentiation, with the majority being well-differentiated tumours (63%).[61,72]

Two studies from Senegal discussed HP SCC, including a study of 66 patients (0.8% of all cases), aged 10 to 86 years, with a mean age of 33,[74] and a study of 15 children, aged 10 to 18 years, with a mean age of 15.[75] The aggregate male-to-female ratio was 0.9:1. Lesion subsite was recorded for

http://dx.doi.org/10.4314/mmj.v27i3.2

Table 1: Included studies of head and neck squamous cell carcinoma of the oral cavity and oropharynx in sub-Saharan Africa since 1990

LOCATION	YEAR	AUTHOR	N	SITES							
				Lip	Oral mucosa	Alveolar ridge	Floor of mouth	Palate	Tongue	OP	Not specified
Central											
DRC	1999	Kayembe[32]	83	14 (17%)	11 (13%)	7 (8%)	6 (7%)	17 (20%)	20 (24%)	-	8 (10%)
Sudan	2010	Ibrahim[33]	192	-	-	-	-	-	-	-	192 (100%)
Sudan	1995	Idris[34]	650	-	-	-	-	-	-	-	650 (100%)
Sudan	2010	Jalouli[35]	217	10 (5%)	73 (34%)	50 (23%)	31 (14%)	6 (3%)	47 (22%)	-	-
Sudan	2012	Jalouli[36]	20	-	-	-	-	-	7 (35%)	-	13 (65%)
Eastern											
Ethiopia	1994	Neway[37]	16	-	-	-	-	-	-	-	16 (100%)
Kenya	2008	Butt[38]	9	-	-	7 (78%)	-	2 (22%)	-	-	-
Kenya	2012	Butt[39]	16	2 (13%)	2 (13%)	2 (13%)	3 (19%)	-	5 (31%)	2 (13%)	-
Kenya	2007	Dimba[40]	187	10 (5%)	32 (17%)	31 (17%)	32 (17%)	25 (13%)	35 (19%)	1 (1%)	21 (11%)
Kenya	1992	Maroo[41]	17	-	7 (41%)	3 (18%)	4 (24%)	2 (12%)	1 (6%)	-	-
Kenya	1995	Onyango[42]	580	53 (9%)	23 (4%)	107 (18%)	31 (5%)	93 (16%)	149 (26%)	-	124 (21%)
Kenya	2004	Onyango[43]	821	86 (10%)	86 (10%)	242 (29%)	63 (8%)	-	220 (27%)	124 (15%)	-
Southern											
RSA	1996	Hille[44]	3070	-	-	-	-	-	-	-	3070 (100%)
RSA	2002	Pacella-Norman[45]	124	-	-	-	-	-	-	-	124 (100%)
Zimbabwe	2006	Chidzonga[46]	313	14 (4%)	33 (11%)	99 (32%)	58 (19%)	28 (9%)	64 (20%)	17 (5%)	-
Western											
Ghana	2009	Parkins[47]	69	5 (7%)	5 (7%)	37 (54%)	4 (6%)	-	12 (17%)	2 (3%)	4 (6%)
Nigeria	1991	Abiose[48]	75	10 (13%)	3 (4%)	20 (27%)	4 (5%)	25 (33%)	11 (15%)	-	2 (3%)
Nigeria	2002	Adewole[49]	58	4 (7%)	10 (17%)	11 (19%)	10 (17%)	-	10 (17%)	-	13 (22%)
Nigeria	2011	Adeyemi[50]	181	9 (5%)	16 (9%)	84 (46%)	8 (4%)	36 (20%)	28 (15%)	-	-
Nigeria	2007	Ajayi[51]	112	2 (2%)	5 (4%)	63 (56%)	8 (7%)	13 (12%)	-	10 (9%)	11 (10%)
Nigeria	2004	Amusa[52]	24	1 (4%)	-	10 (42%)	-	4 (17%)	3 (13%)	6 (25%)	-
Nigeria	1999	Arotiba[53]	246	16 (7%)	13 (5%)	82 (33%)	16 (7%)	57 (23%)	48 (20%)	-	14 (6%)
Nigeria	2006	Arotiba[54]	91	4 (4%)	10 (11%)	14 (15%)	9 (10%)	23 (25%)	23 (25%)	7 (8%)	1 (1%)
Nigeria	2008	Effiom[55]	233	18 (8%)	31 (13%)	128 (55%)	15 (6%)	-	41 (18%)	-	-
Nigeria	2011	Lawal[56]	32	-	-	-	-	-	-	-	32 (100%)
Nigeria	1997	Lawoyin[57]	90	15 (17%)	6 (7%)	7 (8%)	2 (2%)	36 (40%)	22 (24%)	2 (2%)	-
Nigeria	2007	Oji[58]	81	12 (15%)	-	-	17 (21%)	-	24 (30%)	-	28 (35%)
Nigeria	2005	Otoh[59]	28	5 (18%)	2 (7%)	3 (11%)	4 (14%)	8 (29%)	3 (11%)	-	3 (11%)
Nigeria	2000	Rafindadi[60]	115	-	-	-	-	-	-	-	115 (100%)
Total			7750	290 (4%)	368 (5%)	1007 (13%)	325 (4%)	375 (5%)	773 (10%)	171 (2%)	4441 (57%)

DRC = Democratic Republic of Congo
RSA = Republic of South Africa
OP = Oropharynx

http://dx.doi.org/10.4314/mmj.v27i3.2

Table 2: Included studies of head and neck squamous cell carcinoma of the nasopharynx, nasal cavity, and paranasal sinuses in sub-Saharan Africa since 1990

COUNTRY	YEAR	AUTHOR	N	SITES			
				Nasal cavity	Nasopharynx	Maxillary sinus	Not specified
Eastern							
Kenya	1998	Oburra[61]	34	-	2 (6%)	-	32 (94%)
Kenya	1995	Onyango[42]	11	-	-	11 (100%)	-
Southern							
Zimbabwe	2006	Chidzonga[46]	45	-	-	45 (100%)	-
Western							
Nigeria	2010	Afolabi[62]	34	-	34 (100%)	-	-
Nigeria	2004	Amusa[52]	9	-	8 (89%)	1 (11%)	-
Nigeria	1998	Arotiba[63]	73	-	-	73 (100%)	-
Nigeria	2006	Arotiba[54]	70	-	-	70 (100%)	-
Nigeria	2007	Fansula[64]	69	-	-	-	69 (100%)
Nigeria	1999	da Lilly-Tariah[65]	43	-	43 (100%)	-	-
Nigeria	2003	da Lilly-Tariah[66]	22	-	-	-	22 (100%)
Total			410		87 (21%)	200 (49%)	123 (30%)

Table 3: Included studies of head and neck squamous cell carcinoma of the larynx in sub-Saharan Africa since 1990

COUNTRY	YEAR	AUTHOR	N	SITES				
				Supraglottic	Glottic	Subglottic	Transglottic	Not specified
Eastern								
Kenya	1998	Oburra[61]	22	-	-	-	-	22 (100%)
Southern								
RSA	2002	Pacella-Norman[45]	59	-	-	-	-	59 (100%)
Zimbabwe	1993	Tumushime-Buturo[67]	114	30 (26%)	71 (62%)	2 (2%)	-	11 (10%)
Western								
Cameroon	2006	Oyono[68]	10	-	-	-	-	10 (100%)
Nigeria	2004	Amusa[52]	6	-	-	-	-	6 (100%)
Nigeria	2009	Amusa[69]	13	-	-	-	-	13 (100%)
Nigeria	2011	Iseh[70]	20	-	-	-	20 (100%)	-
Nigeria	2002	Nwaorgu[71]	72	10 (14%)	40 (56%)	-	-	22 (31%)
Nigeria	2003	Somefun[72]	36	3 (8%)	21 (57%)	5 (14%)	8 (22%)	-
Togo	1999	Kpemissi[73]	33	-	16 (50%)	-	14 (44%)	2 (6%)
Total			385	43 (11%)	148 (38%)	7 (2%)	42 (11%)	145 (38%)

RSA = Republic of South Africa

http://dx.doi.org/10.4314/mmj.v27i3.2

all patients; 30 (37%) were pyriform sinus, 18 (22%) were posterior pharyngeal wall, seven (9%) were oesophageal introitus, four (5%) were postcricoid, and 22 (27%) were too advanced to determine a primary subsite.

Substance use

Only 527 (7%) of the 7750 OP/OC SCC patients had traditional behavioural risk factors reported, with 35% of them having used tobacco and 32% having used alcohol (Table 4). Data regarding tobacco and alcohol use were available for 335 (87%) of the 385 patients with laryngeal SCC and demonstrated that 56% of patients used tobacco and 56% used alcohol (Table 4). Among hypopharyngeal SCCs, one study of 15 patients (aged 10 to 18 years) noted that no patient used tobacco or alcohol,[75] while another study noted that 13 (20%) of 66 of patients used tobacco, with alcohol use not reported.[74] Duration and amount of use was not consistently reported, and no study specified how tobacco or alcohol use was determined. As shown in Table 4, the proportion of patients who reported alcohol and tobacco use ranged widely across individual studies. A study in South Africa reported 96% and 88% of men using tobacco and alcohol, respectively,[45] while a study from Nigeria reported only 14% use of each substance.[72] Several studies reporting nil alcohol use among HNSCC patients were conducted in predominantly Muslim populations and noted that patients self-reporting alcohol use would not be socially acceptable.

Table 4: Tobacco and alcohol use by country and HNSCC site among included studies from sub-Saharan Africa since 1990

COUNTRY	AUTHOR	SITE	n*	TOBACCO USE n (%)	ALCOHOL USE n (%)
Central					
Sudan	Ibrahim[33]	OP/OC	192	26 (14%)	24 (13%)
Sudan	Jalouli[36]	OP/OC	20	15 (75%)	0 (0%)
Eastern					
Kenya	Butt[39]	OP/OC	16	4 (25%)	5 (31%)
Southern					
RSA	Pacella-Norman[45]	OP/OC	124	97 (78%)	94 (76%)
RSA	Pacella-Norman[45]	Larynx	51	49 (96%)	45 (88%)
Zimbabwe	Tumushime-Buturo[67]	Larynx	114	57 (50%)	57 (50%)
Western					
Nigeria	Adewole[49]	OP/OC	50	30 (60%)	36 (72%)
Nigeria	Lawal[56]	OP/OC	32	8 (25%)	8 (25%)
Nigeria	Oji[58]	OP/OC	81	0 (0%)	0 (0%)
Nigeria	Otoh[59]	OP/OC	12	2 (17%)	1 (8%)
Nigeria	Amusa[69]	Larynx	13	5 (38%)	11 (85%)
Nigeria	Iseh[70]	Larynx	20	20 (100%)	0 (0%)
Nigeria	Nwaorgu[71]	Larynx	68	30 (44%)	47 (69%)
Nigeria	Somefun[72]	Larynx	36	5 (14%)	5 (14%)
Togo	Kpemissi[73]	Larynx	33	26 (79%)	27 (82%)
Total			862	374 (43%)	360 (42%)

*n is the total number of study subjects with data on tobacco and alcohol use. As this data is often incomplete, it may not represent the same "N" presented in tables 1-3.
RSA = Republic of South Africa
OP = Oropharynx
OC = Oral cavity

Another substance reported to be associated with HNSCC is toombak, a fermented and cured tobacco product, commonly used—by placing a portion in the buccal sulcus—in the northernmost regions of sub-Saharan Africa. One Sudanese study reported that 58% of patients with lip, buccal mucosa, and floor of mouth cancer used toombak, while only 19% of patients with tongue, palate, and maxillary sinus cancer reported the same, though rates of toombak use by anatomic site were not reported.[36] A second Sudanese study showed that 67% of patients with OP/OC SCC used toombak.[35] Toombak use was most common in SCC of the oral mucosa, of which 83% of patients were users. Least commonly, only 40% of tongue SCC patients reported toombak use. Oropharynx subsites were not indicated separately. Other studies did not report smokeless tobacco use separately. Another potentially associated substance is kola nut, a stimulant used both socially and ceremonially in many forested regions of sub-Saharan Africa.[76] The raw product can be chewed or the nut can be processed into a beverage. A study from Nigeria observed that four of five patients with OP/OC SCC reported using kola nut.[59]

HIV and HPV

Two studies prospectively identified HIV-infected patients with OC/OP tumours but did not compare this group to HIV-uninfected patients.[38,39] In the first study, 16 HIV-infected patients with OC/OP SCC were identified, including five with SCC of the tongue, three of the floor of the mouth, two of the gingivae, two with OP SCC, two with lip SCC, and two with buccal mucosa SCC. The mean or median age was 32 years, and 44% were male. The authors also found that 63% of cancers were high-grade, poorly differentiated malignancies, and 44% were stage IV at presentation. It was noted that 25% and 31% of patients reported tobacco and alcohol use, respectively.[38] The other study identified nine HIV-infected patients with HNSCC, with a mean age of 36, including two palatal, and seven alveolar ridge tumours.[39] Treatment and outcomes were not described in either study. Other studies anecdotally reported that HIV-infected patients had worse outcomes and were often not surgical candidates. However, no study described patient characteristics or outcomes in HIV-infected and HIV-uninfected HNSCC populations separately for comparison.

One study tested 155 OP/OC SCC specimens from patients in eight countries using PCR for HPV, herpes simplex virus (HSV), and Epstein-Barr virus (EBV).[36] Tumour HPV positivity was highest in Sudan, the only country in sub-Saharan Africa included in the study. No mention was made of patient demographics, site, stage, HIV status, or behavioural risk factors, in relation to tumour HPV status. Additionally, OC and OP tumours were not distinguished and analyzed separately. A second study of 217 OP/OC SCC specimens in Sudan showed that 25% of specimens were positive for HPV, and that more patients reporting toombak use had HPV-positive tumours (27%) than those who did not use toombak (21%), although these differences were not statistically significant.[35] HPV positivity was reported by anatomic subsite, however no clear anatomic trends were described and oropharynx sites were not designated. One study of 15 hypopharyngeal SCCs noted that one patient had severe oral and labial papillomatosis, although HPV confirmatory testing was not performed.[75]

Staging, treatment, and outcome

Stage was reported for 543 (6%) of 8611 patients, and late presentations were common for all anatomic sites. Overall, 3% of HNSCCs were stage I, 6% were stage II, 52% were stage III, and 39% were stage IV. No study described using nasopharyngoscopy, computed tomography (CT), or magnetic resonance imaging (MRI) for staging, and most papers reported that these were not available.

Only one of 28 studies describing OP/OC SCC reported

treatment for 146 patients in Nigeria.[53] Twenty-one patients (14%) declined treatment, 22 (15%) underwent palliative chemotherapy or radiation, and the remainder underwent surgery, chemotherapy, radiation, or a combination with curative intent. Limited outcomes were reported as 113 patients (77%) were lost to follow-up within two weeks of enrolment.

Seven of 11 laryngeal SCC studies discuss treatment, and all reported patients frequently presenting with airway emergencies requiring emergent tracheostomy before definitive treatment. Radiotherapy was used alone or with other treatment modalities in 70% of patients, and outcome data were limited. Patients from studies in Zimbabwe,[67] Togo,[73] Nigeria,[69,70] and Cameroon[68] received radiation therapy. Several studies noted patients who refused treatment, though reasons were not given. With respect to treatment complications, one series reported five of 33 patients developing pharyngocutanenous fistulae.[67] In another series of nine patients, two developed pharyngocutaneous fistulae, while pharyngeal stenosis, stomal stenosis, hypothyroidism, and hypocalcaemia were reported in individual cases.[69] Another series reported pharyngocutaneous fistula in one of three patients who underwent surgery and radiation.[68] One series of five patients who underwent postoperative radiation noted that two died from carotid artery rupture.[70] Rates of mucositis, malnutrition, and infectious complications, common causes of treatment-related morbidity in resource-rich settings, were not reported in any study.

Among HP SCCs,[74,75] two patients (3%) underwent surgery followed by radiation, three patients (4%) underwent surgery alone and 28 patients (35%) underwent radiation alone, while 48 (59%) underwent only palliative tracheostomy or gastrostomy. Within three years of follow-up, 77 patients (95%) had died and the remaining four (5%) were lost to follow-up.

Discussion

To our knowledge, this is the first systematic review of the existing literature of HNSCC in sub-Saharan Africa.

Obstacles to collecting accurate data with respect to age in sub-Saharan Africa are well described.[77] In the studies reviewed, however, age at presentation was approximately 20 years younger for HNSCC patients than in the US.[78,79] Younger age at diagnosis compared with high-income countries has been consistently noted for many cancers in sub-Saharan Africa, and this may reflect biologic differences with respect to cancer pathogenesis and susceptibility, or differences in population age structure, or a combination of both factors.[8]

Established risk factors for HNSCC in high-income countries include smoking, alcohol use, and older age. Overall, of the sub-Saharan HNSCC patients for whom environmental exposures were reported, more than half were non-smokers and denied alcohol use, implying a different set of risk factors compared to high-income countries. However, the data are difficult to analyze. Several studies noted the overall prevalence of tobacco and alcohol use among HNSCC cases, but very few reported the actual number of patients using these substances or the prevalence of tobacco and alcohol use in the general population. Some studies noted that social norms might prevent patients from openly reporting substance use, an inherent limitation of self-reported data.[80]

Clearer descriptions of anatomy and stage would lead to a better understanding of HNSCC in sub-Saharan Africa. In high-income countries, the incidence of HNSCC attributable to tobacco and alcohol is decreasing,[81] while incidence of HPV-associated oropharyngeal SCC is increasing.[82] In the reviewed studies, only 2% of OC/OP cases specified OP as the site, although many papers described tongue or palate tumours that spanned both OC and OP. The lack of advanced imaging and nasopharyngoscopy severely limits the ability of providers to make distinctions regarding anatomic sites and disease stage. The scarcity of staging information may also be due to a lack of familiarity among providers with the complex anatomy and staging of HNSCC. These distinctions have implications in prognosis and treatment. In high-income countries, HPV-positive OP SCC patients have better outcomes than HPV-negative OP patients (and those with HNSCC in other sites)[83,84] and are increasingly treated with deintensification strategies, which include surgery as a single modality.[85] Surgery is available in many sub-Saharan African countries where radiotherapy is not and, therefore, distinguishing OP from OC SCC might influence treatment recommendations.

One study from Sudan reported that two-thirds of OP/OC SCCs were positive for HPV,[36] while a second study from Sudan reported one-quarter of OP/OC SCC to be positive.[35] Another study, which did not meet criteria for inclusion because of missing clinical data, found only two of 146 OP/OC SCCs from black South Africans to be positive for HPV (subtypes 6, 11, 16, 18).[23] Another study of three female patients with laryngeal cancer in Congo noted one tumour to be histologically consistent with HPV, although no confirmatory testing was done.[86,87] These conflicting results underscore the need for further research into the role of HPV in HNSCC in sub-Saharan Africa. HPV vaccination is a high priority for many ministries of health throughout the region, to reduce the immense burden of cervical cancer.[88,89] If HPV is a significant contributor to HNSCC, introducing HPV vaccination may reduce HNSCC burden, in addition to reducing cervical and anal cancer. Long-term monitoring of HNSCC incidence in countries where HPV vaccination has been introduced will be highly informative.

In the US, HIV infection is associated with a two- to three-fold increased risk of HNSCC,[90] although whether this results from increasing mucosal HPV rates and greater susceptibility to HPV oncogenesis, increased tobacco and alcohol use, or both, is uncertain.[91] Limited data suggest that HIV-infected HNSCC patients in sub-Saharan Africa may be younger, with infrequent tobacco and alcohol use, more aggressive cancers, and worse clinical outcomes.[38,39] The effect of antiretroviral therapy (ART) scale-up on cancer incidence overall, and HNSCC incidence specifically, remains uncertain. Further cancer research in settings with high HIV prevalence can clarify these relationships and inform both ART and cancer treatment programmes.

HNSCC is frequently treated with surgery. General surgeons can perform diagnostic biopsies and tracheostomies when indicated, but there is an extreme scarcity of head and neck surgeons to perform curative surgeries for HNSCC in sub-Saharan Africa. A survey of 18 sub-Saharan African countries in 2008 identified one ENT surgeon per million population. If South Africa is excluded, there were 0.6 ENT surgeons per million population,[92] compared with 28 per million population in the US.[93,94] Pathology services are also

lacking, with less than one pathologist per million population in Nigeria,[95] Tanzania,[96] and Uganda,[97] versus 51 per million population in the US.[94,98] Similarly, there are fewer than one medical oncologist per million population in Ethiopia[99,100] and Malawi compared with 43 per million population in the US.[94,101]

Radiation is also a mainstay of HNSCC treatment and can be used alone, in combination with chemotherapy, or following surgery. However, radiotherapy can lead to complications, particularly in settings where treatment may be administered using older units, without modern techniques to minimize toxicity.[102] No studies reported rates of mucositis, infection, or malnutrition in patients receiving radiotherapy, although these are frequently observed complications in resource-rich settings. Even when safely administered, radiotherapy units are severely limited throughout sub-Saharan Africa, which has only 88 radiotherapy facilities overall, of which 53 are in South Africa or Nigeria. Twenty-seven countries within the region have no radiotherapy at all, and of the countries that do administer radiotherapy, most have only a single operational unit.[103]

HNSCC is a complex disease that is incompletely described in sub-Saharan Africa. As with many other disease entities, improvement in medical infrastructure will improve diagnosis, treatment, and outcomes.

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