

Challenges of Human Papillomavirus Infection and Associated Diseases in Low-Resource Countries

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• **Context.**—The prevalence of human papillomavirus (HPV) infection varies worldwide. The high-risk viruses are usually associated with cancers of the cervix, vagina, and vulva in women, cancer of the penis in men, and cancers of the anus, tonsils, oropharynx, and base of the tongue in both sexes.

Objectives.—To review literature about the challenges and burden associated with HPV infection in low-resource (ie, developing) countries, focusing on sub-Saharan Africa. To review the prevention, incidence, prevalence, morbidity, and mortality of HPV infections in sub-Saharan Africa. To review the therapy and management of HPV infections in low-resource countries in comparison to developed countries.

Human papillomaviruses (HPVs) are DNA viruses that belong to the family Papillomaviridae with up to 150 subtypes sequenced.¹ They are the first known human tumor viruses associated with benign epithelial neoplasms. From the severity of infections, the papillomaviruses can be subdivided into low-risk and high-risk types.² The high-risk HPV subtypes have been associated or linked to several human cancers of epidemiologic significance.² Most HPV low-risk types are associated with asymptomatic infections or benign papillomas in individuals with uncompromised immune systems.² Though not uncommon, a few low-risk HPV subtypes have been associated with cancers.²

The high-risk virus subtypes have been divided by the World Health Organization into 2 categories on the basis of risk of progression to cancers subsequent to infection.² The first group is “category 1/high risk” and includes 12 HPV subtypes, namely, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59.^{3–5} The second group is “possibly cancer causing” and includes subtypes 68 and 73.^{3–5} The high-risk viruses are usually associated with cancers of the cervix, vagina, and vulva in women, cancer of the penis in men, and cancers of

Data Sources.—Peer-reviewed literature and experience of some of the authors.

Conclusions.—Sub-Saharan Africa has high HPV infection prevalence rates, with predominance of high-risk subtypes 16, 18, and 45. The difficulty of access to health care has led to higher morbidity and mortality related to HPV-related cancers. Improvement in screening programs will help in monitoring the spread of HPV infections. Survival studies can be more informative if reliable cancer registries are improved. HPV vaccination is not yet widely available and this may be the key to curtailing the spread of HPV infections in resource-poor countries.

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the anus, tonsils, oropharynx, and base of the tongue in both sexes.² It is important to note that these high-risk HPVs do not cause cancer in all infected individuals, as most of these individuals remain cancer free.^{6,7}

INCIDENCE AND BURDEN OF HPV IN LOW-RESOURCE COUNTRIES WITH EMPHASIS ON SUB-SAHARAN AFRICA

HPV is a very common sexually transmitted infection with global prevalence. A meta-analysis of HPV testing in cervical cytology samples showed prevalence ranging from 11% to 12%.⁸ Moreover, this prevalence varies regionally with a higher prevalence in the less developed countries than in the developed countries.⁹ Sub-Saharan Africa, Latin America, the Caribbean, Eastern Europe, and Southeast Asia account for the bulk of HPV-associated diseases.⁹ Sub-Saharan Africa, home to 9% of the world’s female population older than 15 years, has the highest prevalence rate of HPV-associated diseases in the world and accounts for 14% of the world’s incident cases of cervical cancer.^{10,11}

Although most Sub-Saharan African countries have cervical cancer ranking first or second (after breast cancer) in cancer incidence, the prevalence rates differ among various sub-Saharan African countries.¹² This unfortunate statistic also continues in the mortality rate, with cervical cancer being the leading cause of cancer deaths in Africa (50,223 cases per year). This figure accounts for 18% of the entire world’s invasive cancer deaths.¹² Overall age-standardized incidence and mortality rates for invasive cervical cancer with regard to sub-Saharan Africa are 31.7 and 22.5 per 100,000 women, compared to 9.1 and 3.1, respectively, in more developed countries.¹²

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Globally, HPV prevalence shows an age-related trend, with higher rates seen in women younger than 25 years, and a steady decline at older ages. However, in African populations, no age-related decline is noted.¹³ HPV 16 and 18 have been identified as the predominant oncogenic types causing 70% of global cervical cancers,¹⁴ which is comparable to 67.7% of African cases.^{15–18} In Africa, the prevalence rates of HPV in women are high with 29.3% with normal cervical cytology, 46.5% with atypical squamous cell of undetermined significance, 74.2% with low-grade squamous intraepithelial lesion, 84.6% with high-grade squamous intraepithelial lesion, and 89.5% with invasive cervical cancer.¹⁶ In cases of invasive cervical cancer, HPV 45 is the third most common type in Africa.^{12,14,15,19,20} Each subregion in Africa studied showed that the 3 subtypes, namely, 16, 18, and 45, remained most common for invasive cervical cancer despite differences in regional prevalence.²¹

De Vuyst et al¹² reported that lack of screening programs in sub-Saharan Africa is evident by the rise in the age-specific incident rates of cervical cancer at the age of 40 to 44 years (36 per 100,000 and more), reaching a peak above 50 per 100,000 women around the age of 55 to 65 years.¹² This is higher than what was obtained in developed countries with effective screening programs, such that maximal rates are 20 per 100,000 at around 40 years of age.^{8,12} Survival studies in Africa are hampered by the lack of sustained reliable cancer data from cancer registries.^{9,12} However, in 3 sub-Saharan African countries, age-standardized relative survival after a diagnosis of invasive cervical cancer was low when compared to other subregions worldwide.¹² Invasive cervical cancer is the most important cause of years of life lost due to cancer in women in the region (20% of all years of life lost).^{9,12} A host of sociocultural factors and practices may suggest the reason for subregional differences among HPV prevalence in Africa. These may include polygamy, risky sexual behavior, early sexual debut, unsafe sex practices, and multiple sexual partners.^{9,12} The numerous areas of armed conflict with gender-based violence where rape is often used as a weapon of war is also a factor to be considered in Africa.¹²

HPV is more easily acquired after infection with the human immunodeficiency virus (HIV). HIV infection is still very prevalent in sub-Saharan Africa with an estimated 1.4 million new HIV infections in 2014.²² Studies show a higher prevalence of cervical and anal HPV infection in HIV-infected patients than in HIV-uninfected individuals.¹² Other observational studies have shown that HIV-infected women have a higher risk of incidence and progression of HPV than HIV-uninfected women.¹² Multiple HPV types are very common in precancerous lesions in HPV-affected populations; in women infected with HPV, HPV 58 is the second most dominant strain after HPV 16.²³

Worldwide, penile cancer is rare, with higher incidence rates in less developed countries, correlating with the incidence of cervical cancer.²⁴ Penile cancers make up 10% of male cancers in Africa, South America, and Asia.²⁴ In Nigeria, penile invasive squamous cell carcinoma makes up less than 1% of malignancies among men and occurs at a median age of 60 years or older.²⁵ Worldwide, 40% of penile cancers are attributable to HPV infection.²⁶ The prevalence of penile HPV infection in reports worldwide ranges from 29% to 82% and varies by country, population studied, and area of genitalia sampled.²⁷ Although precancerous lesions of the penis (ie, penile intraepithelial neoplasia) are rare, HPV DNA positivity is observed in 60% to 100% of these

lesions.²⁵ HPV types 16 and 18 are the most common genotypes detected in squamous cell carcinoma of the penis.²⁸ Penile HPV infection is dependent on high-risk sexual behavior including lifetime number of sexual partners, number of recent sexual partners, age at first intercourse, as well as sexual frequency.^{29–33} Even with condom use, transmission of HPV has been documented via unprotected areas of genital skin.²⁷ Evidence favors circumcision as a protective factor against HPV infection, with risk reduction ranging from 60% to 80%.^{29,34}

Regions of high incidence of head and neck cancer include Asia, Central and Eastern Europe, and South America.^{24,35} There is a worldwide increase in oropharyngeal cancers, including cancers of the base of the tongue, tonsils, and other parts of the oropharynx.^{36,37} This contradicts the falling incidence of smoking-related head and neck cancers and is believed to be due to the “virus-related epidemic.”³⁶ HPV is regarded as an independent risk factor in the development of head and neck squamous cell cancers aside from tobacco and alcohol.^{38–41} The 2 most prevalent types of HPV overall in oral carcinomas are types 16 and 18.³⁹ Occasionally, HPV types 6 and 11 may be identified in some oral carcinomas as well as in some laryngeal carcinomas.³⁶

In South Africa, a pilot study showed a low prevalence rate (5.6%) of oral and oropharyngeal high-risk HPV (types 18 and 68) when compared to worldwide rates.⁴² The prevalence of the high-risk HPV types was found to be positively associated with the number of oral sexual partners.⁴² The low prevalence of high-risk HPV types in this study was associated with the uncommon practice of oral sex among the men studied in these regions.⁴²

Head and neck cancers in Nigeria show a peak incidence in the fourth decade of life with a male predominance and a younger age of onset than in white individuals.^{43–53} The explanation for this finding might be rooted in genetic, behavioral, and socioeconomic risk factors.⁴³ Various risk factors in Nigeria have been identified including kola nuts, tobacco, farming, viral infections (HPV and Epstein Barr virus), alcohol, and smoking.^{44,54–58} These risk factors vary depending on the geographic location within the country. In Nigeria, smoking cigarettes, and chewing of kola nuts and tobacco have been implicated in the development of carcinoma in the oral cavity.⁴³ Pathogenesis of oral cancers has been attributed to the permissive palatal mucosal keratinization effects of kola nut in cigarette smokers.⁴³ In parts of Nigeria where most patients were nonsmokers, demographic evidence points to some viral infections being implicated in the etiology, but further evidence on the role of HPV is lacking.^{54,56} Epithelial malignancies were the most common head and neck cancer subtypes, with squamous cell variants being the most histologically diagnosed within Nigeria.^{43–46,48,49,58,59}

CHALLENGES

In Nigeria, there is poor utilization of cervical screening used in the prevention of cervical cancer, in great part due to the paucity of well-organized, high-quality screening programs.⁶⁰ Furthermore, most young Nigerian women have little knowledge or awareness of cervical cancer. Many of these women are ignorant of the risks of early sexual exposure.⁶¹ This is alarming considering that among female undergraduate students in Ibadan, South West Nigeria, 51.7% of respondents had their first sexual experience before 20 years of age.⁶² Of interest to note is that most of

these women have never had a pelvic examination.⁶³ For these reasons, most women (97.9%) have never been screened for cervical cancer.⁶¹ Absence of available screening services (44.2%) is the most important reason, closely followed by lack of information (40.7%).⁶¹ Other reasons included a poor or absent decision-making ability (34.2%), cost of screening services when available (30.1%), lack of husband support (28.4%), distance from the screening centers (23.5%), and the perception of invasion of one's privacy (18.7%).⁶¹ There was a significant association between the level of education and the women's willingness to use cancer screening services.⁶¹

Many countries have introduced alternatives to cervical cytology screening in an attempt to combat HPV-related diseases.⁶⁴ This includes HPV DNA testing, which provides a higher throughput, higher sensitivity, and a higher negative predictive value than cervical cytology.⁶⁴ This has been carried out with success in Nigeria and Uganda, with HPV DNA testing implemented on less expensive platforms by established personnel.⁶⁴ HPV point-of-care testing may also serve to ease delivery of services in areas with limited laboratory access. HPV vaccination offers a way for primary prevention with significant benefits. Vaccination is recommended for preadolescent and adolescent females with the pool of candidates now being expanded to males. Two safe and highly efficacious vaccines have been licensed for HPV worldwide and are available in many countries.^{64,65} The vaccines prevent persistent HPV infections, precancerous and cancerous cervical lesions, and precancerous and cancerous lesions in the anogenital tract attributable to HPV types 6, 11, 16, and 18.⁶⁴ The vaccines include the quadrivalent vaccine (Gardasil, Merck & Co, Whitehouse Station, New Jersey) active against HPV types 6, 11, 16, and 18 and bivalent vaccine (Cervarix, GlaxoSmithKline Biologicals, Rixensart, Belgium) active against HPV types 16 and 18.⁶⁵ These vaccines cover only selected strains of high-risk HPV with no cure for infected patients. They may, however, prevent infected women with HPV lesions from acquiring new ones.⁶⁴ Thus, these vaccines do not replace the importance of cervical cancer screening.⁶⁴ The first of these vaccines was licensed for use by the US Food and Drug Administration in the United States in 2006 and they were available in Nigeria by 2009. However, owing to the high cost of the vaccines and poor knowledge about HPV infection, the use of these vaccines is not widespread.⁶⁶

In 2011, six pilot centers were commissioned by the government of Nigeria to give the HPV vaccines in addition to those offered by private facilities. The vaccines were approved for administration in females between the ages of 9 and 26 years.⁶⁶ This was in keeping with the Nigerian National Cervical Cancer Control Policy in 2010, which recommended vaccination with the HPV vaccines against genotypes 16 and 18, which are responsible for most cases of cervical cancer.⁶⁶ Presently, there is no national implementation plan for the HPV vaccines in Nigeria.⁶⁶

Global Donors through the GAVI INITIATIVE (Global Alliance for Vaccine and Immunization) offer both Gardasil and Cervarix vaccines at subsidized prices to some low-income countries.^{67,68} However, Nigeria does not qualify for this program.⁶⁸

Acceptability issues may be a concern in countries within sub-Saharan Africa (Nigeria inclusive) with conservative sociocultural values, as the vaccine may be seen as a license for acceptability of premarital sex. Kalell⁶⁹ reports that issues to be addressed in developing countries include unfounded

rumors that immunization with HPV vaccines sterilizes preadolescent and adolescent girls, a lack of safety data in relation to oral contraceptive drugs, hormone-related therapy, and other prescribed drugs used in menstruating and menopausal women.⁶⁹ There is also worry over the purported high level of aluminum salts in the vaccines that may purportedly lead to the disruption of the immune system of infants and children, leading to chronic illness.⁶⁹ These issues mentioned above have not been helped by the growing list of countries (including the governments of Japan, Ireland, Colombia, and Spain) that have constituted investigations into the perceived effects of these vaccines after advocacy from human rights groups.⁶⁹

CONCLUSIONS

The issues highlighted above are mutual to Nigeria and most sub-Saharan countries. Long-term strengthening of national adolescent vaccination policies, adapting vaccine delivery strategy to local resources, and integration of HPV vaccination and screening procedures may help resource-poor countries curtail the spread of HPV infection and minimize the burden of infection.^{9,10,70} Vaccination of teenage females and males may prove to be helpful in primary prevention of HPV-related diseases and may be the key to significantly reducing HPV infections in resource-poor countries. Mothers play a crucial role in making informed decisions, as effective coverage of the vaccines is dependent on parental approval and acceptance.⁷¹ Screening and vaccination program evaluations should also be developed and surveillance systems should be introduced. Health promotion and education in these African countries should also be intensified with the indigenous population educated on the mode of infection, nature, and prevention of HPV-related diseases.⁷⁰ Health services in low-resource countries should be reoriented with incorporation of affordable diagnostic procedures.⁷⁰

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