Human papillomavirus prevalence and type distribution in invasive cervical cancer in sub-Saharan Africa

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Abbreviations: ADC= adenocarcinoma; CI= confidence interval; DEIA= DNA enzyme immune assay; FIGO= Federation of Gynecology and Obstetrics; HPV= human papillomavirus; ICC= invasive cervical cancer; $LiPA_{25}$= line probe assay using 25 type-specific hybridization probes; SCC= squamous cell carcinoma; PCR= polymerase chain reaction;

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Novelty and impact of the work: This was the first study conducted in sub-Saharan Africa using standardized and validated methods for human papillomavirus (HPV) detection and typing, and centralized pathology review for confirmation of the histological diagnosis. In women with invasive cervical cancer from Ghana, Nigeria, and South Africa, the HPV-positivity rate was 90.4%; HPV16 and HPV18 were the most frequently detected types. These results suggest that HPV vaccination may reduce the invasive cervical cancer disease burden in sub-Saharan Africa.

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Abstract

In sub-Saharan Africa, invasive cervical cancer (ICC) incidence and mortality are among the highest in the world. This cross-sectional epidemiological study assessed human papillomavirus (HPV) prevalence and type distribution in women with ICC in Ghana, Nigeria, and South Africa. Cervical biopsy specimens were obtained from women aged ≥21 years with lesions clinically suggestive of ICC. A questionnaire was used to evaluate the HIV status and the medical, sexual, and reproductive history of women. Histopathological diagnosis of ICC was determined by light microscopy examination of hematoxylin and eosin stained sections of paraffin-embedded cervical specimens; samples with a confirmed histopathological diagnosis underwent HPV DNA testing by polymerase chain reaction. HPV-positive specimens were typed by reverse hybridization line probe assay. Between October 2007 and March 2010, cervical specimens from 659 women were collected (167 in Ghana, 192 in Nigeria, and 300 in South Africa); 570 cases were histologically confirmed as ICC.

The tumor type was identified in 551/570 women with ICC; squamous cell carcinoma was observed in 476/570 (83.5%) cases. The HPV-positivity rate in ICC cases was 90.4% (515/570). In ICC cases with single HPV infection (447/515 [86.8%]), the most commonly detected HPV types were HPV16 (51.2%), HPV18 (17.2%), HPV35 (8.7%), HPV45 (7.4%), HPV33 (4.0%), and HPV52 (2.2%). HPV type distribution appeared to differ according to tumor type and HIV status. In conclusion, HPV16 and HPV18 were the most frequently detected types in women with ICC in sub-Saharan Africa and implementation of HPV vaccination may reduce the ICC disease burden in this region.

Introduction

In African women, invasive cervical cancer (ICC) is the second most common cancer and leading cause of cancer death.[1,2] The high incidence of ICC in developing countries may be explained by low awareness and inability to successfully implement nationwide screening programs.[3] The number of deaths from ICC is nearly 10 times greater in these countries than in developed regions, and this is mainly due to lack of access to anti-cancer therapy combined with late presentation.[3,4] In sub-Saharan Africa, over 70,000 new cases occur annually, and ICC is responsible for 25% of all female cancers and has an estimated overall age-standardized incidence rate of 31.0 per 100,000 women.[1,2,4–6] This is far higher than the overall age-standardized incidence rate of 11.9 per 100,000 women observed in Europe.[5,6]

Persistent infection with an oncogenic human papillomavirus (HPV) type has been identified as the necessary cause for the development of ICC.[3,7–9] More than 40 different HPV types are known to infect the genital tract and 15 of these have been classified as oncogenic to humans.[5,10–14] Women are exposed to genital HPV infections when they become sexually active and remain at risk throughout their lives.[15,16] The necessary role of HPV infection in the development of ICC provides an opportunity to reduce disease burden through early

diagnosis using HPV testing and prevention programs including prophylactic HPV vaccination.

The primary objectives of this study were to assess the prevalence of HPV in adult women with ICC in sub-Saharan Africa (Ghana, Nigeria, and South Africa) and the distribution of the most commonly detected HPV types. This is the first study using a standardized protocol for sampling and HPV typing to look specifically at HPV type distribution in sub-Saharan African women with ICC, which is important to evaluate the potential impact of prophylactic vaccines in this region.

Material and Methods

Study design and population

This cross-sectional, multicenter, epidemiological study was conducted in women aged ≥21 years from Ghana, Nigeria, and South Africa, who had cervical lesions clinically suggestive of ICC. Women who had previously received chemo- or radiotherapy for cervical cancer were excluded. Cervical biopsy specimens were obtained by a gynecologist as part of routine investigative procedures at the participating hospital. Women who underwent a cervical biopsy received a questionnaire to evaluate their socio-demographic characteristics, medical/gynecological history, HIV status, smoking habits, sexual and reproductive history, and contraception use. Sections of tissue blocks were used by a pathologist for the histopathological diagnosis of ICC (squamous cell carcinoma [SCC], adenocarcinoma [ADC], and other tumor types). In women diagnosed with ICC, the Federation of Gynecology and Obstetrics (FIGO) cancer stage was determined by clinical staging.[17]

Tissue blocks from women diagnosed with ICC were shipped to the central laboratory (DDL Diagnostic Laboratory, Rijswijk, The Netherlands) for confirmatory diagnosis by a gynecological histopathologist, who was blinded to the initial diagnosis. If the presence of

ICC, the tumor type, and the suitability of the sample for further examination were confirmed, the tissue block was sent for HPV DNA detection and typing. If the presence of ICC and the tumor type were not confirmed, a second histopathologist at the central laboratory reviewed the sections; the diagnosis was determined by simple majority rule. No further study procedures were performed on tissue blocks if the diagnosis of ICC was not confirmed or if the tissue blocks were not appropriately stored.

The study was approved by the appropriate Institutional Review Board and/or Independent Ethics Committee of each participating center and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Informed consent was obtained from women prior to any study procedure on clinical specimens.

Laboratory procedures

Cervical biopsy specimens obtained were immediately fixed in 10% buffered formalin, processed for paraffin wax embedding, and checked for quality. Biopsy samples that could not be immediately sent for paraffin embedding were stored in 10% buffered formalin in a firmly-closed screw-top container at room temperature (15–25°C) in the dark for a maximum of 7 days. Histopathological diagnosis of ICC was determined by light microscopy examination of hematoxylin and eosin stained sections of cervical specimens. The remainder of tissue blocks from women diagnosed with ICC was stored at a temperature of 4–35°C before being shipped to the central laboratory.

At the central laboratory, samples with a confirmed histopathological diagnosis of ICC underwent HPV DNA typing using SPF_{10} PCR-DEIA-$LiPA_{25}$ version 1 system (Labo Biomedical Products, The Netherlands; based on SPF_{10} licensed Innogenetics technology).[18,19] Total DNA was isolated and extracted using a proteinase K lysis procedure. DNA was amplified by SPF_{10} and generic amplification products were detected by DNA probe

hybridization and DNA enzyme immune assay (DEIA). HPV-positive specimens were typed by reverse hybridization line probe assay using 25 type-specific hybridization probes ($LiPA_{25}$), which detected 14 high-risk (HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, HPV52, HPV56, HPV58, HPV59, HPV66, HPV68/73) and 11 low-risk (HPV6, HPV11, HPV34, HPV40, HPV42, HPV43, HPV44, HPV53, HPV54, HPV70, HPV74) types, as previously described.[20] Samples that were DEIA-positive and $LiPA_{25}$-negative were classified as HPV untypeable. Positive and negative controls were used to monitor DNA isolation, polymerase chain reaction (PCR) amplification, HPV detection, and typing procedures. The DNA of HPV-negative samples was diluted tenfold and testing was repeated to rule out inhibitors in the sample being responsible for negative results rather than true absence of HPV.

Statistical analysis

Three cohorts were used for analysis: the total enrolled cohort included all women enrolled in the study; the histologically confirmed cohort included all enrolled women with confirmed diagnosis of ICC; and the HPV-positive cohort included all women from the histologically confirmed cohort with a positive HPV DNA status.

In each country, 238 enrolled women with ICC were needed to reach the target of 193 HPV-positive women, which allowed for possible histological misclassification and PCR inadequate samples. Sample size calculations demonstrated that with 193 HPV-positive women per country, the precision of the 95% confidence interval (CI) for each HPV type would not exceed 6% for percentages <20% and 5% for percentages <10%.

Demographic characteristics, parity, pregnancy, smoking history, HIV status, and tumor type were tabulated overall and per country. Contraception use and distribution of FIGO cancer stages were tabulated overall, per country, age group, and HIV status. In the HPV-

positive cohort, proportions of single and multiple HPV infections were calculated overall, per country, and HIV status with their exact 95% CI. In women with single HPV infection, percentages of women infected by each HPV type were tabulated overall, per country, tumor type, and HIV status with their exact 95% CI. In women with multiple HPV infections, percentages of women infected by each HPV type were also tabulated overall and per country with their exact 95% CI. In an exploratory analysis, potential differences ($p<0.05$) in proportions of women infected with HPV16 and HPV18 were evaluated between countries. All statistical analyses were performed using SAS® software (version 9.2).

Results

Demographics

Between October 2007 and March 2010, biopsy specimens from 659 women were included in the total enrolled cohort; 167 in Ghana, 192 in Nigeria, and 300 in South Africa. Among women with data available, 98.8% (637/645) reported having been pregnant at least once, 5.2% (34/648) reported that they were using contraception at the enrolment time, 4.9% (32/648) were sterilized, and 43.6% (267/613) had used contraception in the past (data not shown). Parity was 0 in 3.8% (25/656) of women, 1–2 in 17.1% (112/656) of women, 3–5 in 38.1% (250/656) of women, and ≥6 in 41.0% (269/656) of women. Among women with data available, 84.7% (555/655) reported that they had never smoked tobacco and 9.1% (50/551) were current smokers.

Overall, 570/659 (86.5%) cases were histologically confirmed as ICC (Table 1). The histologically confirmed cohort included 97.6% (163/167) of women from the total enrolled cohort in Ghana, 93.2% (179/192) in Nigeria, and 76.0% (228/300) in South Africa. The majority of women (92.3%; 526/570) were of African ethnic background and their median age was 55 years. In women from the histologically confirmed cohort (N=570), SCC

accounted for 83.5% (476/570) of cases, ADC for 7.5% (43/570) of cases, other tumor types for 5.6% (32/570) of cases, and the specific tumor type could not be identified in 3.3% (19/570) of cases. Respective proportions of each tumor type are presented per country in Table 1.

In the histologically confirmed cohort, 11.9% (68/570) and 30.2% (172/570) of women were HIV-positive and HIV-negative, respectively, while the HIV status of 57.9% (330/570) of women was unknown (not tested for HIV) (Table 1). Proportion of women with unknown HIV status seemed higher in Ghana (158/163; 96.9%) and Nigeria (147/179; 82.1%) than in South Africa (25/228; 11.0%). In women for whom the HIV status was known, HIV positivity rates were 60% (3/5) in Ghana, 28.1% (9/32) in Nigeria, and 27.6% (56/203) in South Africa.

The two most frequently determined FIGO cancer stages were IIIB (192/570; 33.7%) and IIB (173/570; 30.4%). Stage IIIB was more frequently identified than stage IIIA in Ghana (27.6% versus 8.6%) and South Africa (51.8% versus 0.9%), while in Nigeria the opposite was observed (16.2% versus 26.3%). The distributions of FIGO cancer stages per age stratum, tumor type, and HIV status are given in Table 2.

HPV type distribution

In the histologically confirmed cohort, the HPV-positivity rate was 90.4% (515/570 women); 93.9% (153/163) in Ghana, 84.9% (152/179) in Nigeria, and 92.1% (210/228) in South Africa. Proportions of HPV-positive cases in women with SCC and ADC were 95.2% (453/476) and 76.7% (33/43), respectively.

In the HPV-positive cohort, 447/515 women had a single HPV infection (86.8% [95% CI 83.6–89.6%]), 57/515 women had multiple HPV infections (11.1% [8.5–14.1%]), while 11/515 women were infected with untypeable HPV type(s). Multiple HPV infections were detected in 29/153 (19.0% [13.1–26.1%]) HPV-positive women in Ghana, 6/152 (3.9% [1.5–

8.4%]) HPV-positive women in Nigeria, and 22/210 (10.5% [6.7–15.4%]) HPV-positive women in South Africa. In women with single and multiple HPV infections, the most commonly detected HPV types were HPV16 (50.7% [46.3–55.1%]), HPV18 (19.2% [15.9–22.9%]), HPV45 (10.1% [7.6–13.0%]), HPV35 (9.7% [7.3–12.6%]), HPV33 (5.0 [3.3–7.3%]), and HPV52 (4.5% [2.9–6.6%]).

Across the three countries, the proportion of HIV-positive women who were HPV-positive was 66/68 (97.1% [89.8–99.6%]) and the proportion of HIV-negative women who were HPV-positive was 156/172 (90.7% [85.3–94.6%]). Multiple HPV infections were detected in 8/66 (12.1% [5.4–22.5%]) HIV-positive women and in 13/156 (8.3% [4.5–13.8%]) HIV-negative women. In South Africa, where the HIV status of almost 90% of women was known, 54/56 (96.4% [87.7–99.6%]) HIV-positive women and 134/147 (91.2% [85.4–96.2%]) HIV-negative women were HPV-positive. In that country, 8/54 (14.8% [6.6–27.1%]) HIV-positive and 12/134 (9.0% [4.7–15.1%]) HIV-negative women had multiple HPV infections.

In the 447 women with single HPV infection, HPV16 accounted for 51.2% of cases, followed by HPV18 (17.2%), HPV35 (8.7%), HPV45 (7.4%), HPV33 (4.0%), and HPV52 (2.2%) (Table 3). Although HPV16 was the dominant HPV type in all countries, exploratory analyses suggested that the relative proportion of women with single HPV16 infection was higher in Ghana than in South Africa. The relative proportion of women with single HPV18 infection tended to be greater in Ghana than in Nigeria.

The most commonly detected HPV types in the 394 women with SCC with single HPV infection were HPV16 (53.8%), HPV18 (15.0%), HPV35 (9.4%), and HPV45 (7.1%) (Table 4). The most commonly detected HPV types in the limited sample of women with ADC (N=27) with single HPV infection were HPV18 (29.6%), HPV16 (22.2%), and HPV45 (18.5%).

Respective contributions of HPV16 and HPV18 were 49.1% (27/55) and 27.3% (15/55) in HIV-positive women compared with 51.4% (72/140) and 15.0% (21/140) in HIV-negative women with single HPV infection (Table 5).

The most frequently detected HPV types in the 57 women with multiple HPV infections, in whom types that actually caused the lesion were not identified, were HPV16 (56.1%), HPV18 (38.6%), HPV45 (33.3%), HPV52 (22.8%), and HPV35 (19.3%) (Table 6). In these women, HPV52 tended to be identified more frequently in Ghana (31.0%) and Nigeria (33.3%) than in South Africa (9.1%).

Discussion

This cross-sectional study assessed the HPV type distribution in women diagnosed with ICC in sub-Saharan. This is the first study conducted in Africa using standardized and validated methods for HPV DNA detection and testing, as well as centralized pathology review for confirmation of the histological diagnosis.

The vast majority (90.4%) of cervical specimens collected in women with histologically confirmed ICC were HPV-positive. The most frequently detected HPV types in women with single and multiple HPV infections were HPV16 (50.7%), HPV18 (19.2%), HPV45 (10.1%), HPV35 (9.7%), HPV33 (5.0%), and HPV52 (4.5%), showing that HPV45 is a relatively important type in sub-Saharan Africa. This HPV type distribution is in line with that reported in a global, retrospective, cross-sectional study conducted in 544 African women with ICC and in other studies conducted in Africa, except for HPV35 that seemed more frequently identified here than previously.[20–23] These results are also consistent with a recent international meta-analysis, including 30,848 women worldwide, in which 89.9% of women with ICC were HPV-positive and HPV16 and HPV18 accounted for 73% of HPV-positive cases.[22] Here, HPV16 predominated in women with SCC, while HPV18, 16, and 45 were

frequently identified in the limited number of women with ADC. This is in keeping with the results of other recent studies of HPV type distribution in SCC and ADC.[21,24]

In this study, the prevalence of HPV infection was higher in HIV-positive women, who are more likely to have multiple HPV infections. Although the total number of HIV-positive women was relatively low and the overall proportion of women with unknown HIV status was high in the present study, this observation is in line with previous findings on the prevalence of HPV infection in HIV-positive women with ICC in sub-Saharan Africa.[25-26] Moreover, in South Africa, where the HIV status of almost 90% of women was known in the present study, the prevalence of single and multiple HPV infections was also higher among HIV-positive women than among HIV-negative women. This observation may be explained by the common sexual mode of transmission of HPV and HIV or by the potential reactivation of latent HPV infections as a result of immune suppression. Although previous studies reported that HPV52 was more frequently identified in HIV-positive than in HIV-negative women, the number of HIV-positive women was too low in the present study to confirm this finding.[27–29]

Estimating the fraction of ICC attributable to each HPV type is increasingly complicated by the detection of multiple HPV infections; considering cases with multiple HPV infections could introduce bias in the type distribution analysis, while restricting the analysis to single HPV infections may underestimate the relative contribution of individual HPV types. Here, analyses of HPV type distribution were presented first for women with single infection and then for women with multiple infections. In cases with multiple infections, the actual HPV type causing the lesion has not been investigated, which is a limitation of this study. However, two HPV types seemed more frequently detected in the limited number of women with multiple infections than in women with single infection: HPV52 (22.8% versus 2.2%) and HPV45 (33.3% versus 7.4%).

Two vaccines containing virus-like particles are currently licensed in various countries: a bivalent vaccine (*Cervarix*®, GlaxoSmithKline, Rixensart, Belgium) formulated with the AS04 adjuvant system offering protection against HPV16 and HPV18 and a quadrivalent vaccine (*Gardasil*™, Merck and Co., Inc, Whitehouse Station, New Jersey, USA) formulated with an aluminum hydroxyphosphate sulfate adjuvant offering additional protection against HPV6 and HPV11, two non-oncogenic HPV types which may give rise to non-malignant lesions but have limited bearing on the global ICC disease burden.[30,31] Previous studies have shown that both vaccines had clinically acceptable safety profiles, were highly immunogenic and efficacious, and offered protection against infection with the vaccine types and their associated cytological and histological outcomes in adolescent girls and young women.[32-49] *Cervarix*® has demonstrated >90% vaccine efficacy against cervical intraepithelial neoplasia grade 3 or worse, irrespective of the HPV type, and also cross-protective efficacy against four oncogenic non-vaccine types (HPV31, HPV33, HPV45, and HPV51).[46,47,49] *Gardasil*™ has also demonstrated cross-protective efficacy against HPV31.[50] Here, HPV16 and HPV18 accounted for 68.4% of ICC cases in women with single HPV infection, ranging from 65.5% of cases in South Africa to 74.4% of cases in Ghana.

Strengths of this study included the standardized protocol used in the three countries, the central histopathological assessment with blinded expert review, the well-validated, highly-sensitive method used for HPV DNA detection, and the typing process enabling detection of a broad spectrum of HPV types. This study addresses an important data gap since there is virtually no good epidemiological evidence of HPV type distribution in women with ICC in sub-Saharan Africa, but was limited by the fact that it only included one South- and two West-African countries, with no East-African representation. This study was not powered to observe differences between regions of sub-Saharan Africa and the results of the exploratory comparison between countries in terms of relative contributions of HPV16 and HPV18 in ICC

should be interpreted with caution. The high rate of women with unknown HIV status, the fact that 54/66 HIV-positive women were from South Africa, and the lack of confirmation of HIV status in the other countries might have introduced potential bias. Limitations included also the low number of ADC cases, the relatively high proportion of women in whom the HPV type could not be determined, and the absence of identification of the HPV type actually causing the lesion in women with multiple infections.

In conclusion, HPV positivity rates were high as expected in women with ICC in sub-Saharan Africa, and HPV16, HPV18, HPV35, HPV45, HPV33, and HPV52 were the most commonly detected types in women with single HPV infection. Implementation of prophylactic HPV vaccination in adolescent girls and women may reduce the disease burden of ICC in this region.

Cervarix is a registered trademark of the GlaxoSmithKline group of companies
Gardasil is a trademark of Merck & Co., Inc.

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Conflicts of interest: LD declares to have received institutional grants from GlaxoSmithKline group of companies and also declares to have received institutional grants from another pharmaceutical company (there is also one pending grant). Further, LD declares to have received payment for lectures and also receives royalties for a book chapter. IA declares to have received payment from GlaxoSmithKline group of companies for travel, food and accommodation and also declares to have served as a member of IDMC for other clinical studies. IA also has received payment for participating at a workshop. RA declares to have received payment from GlaxoSmithKline group of companies towards administrative and laboratory fees and also declares to have received payment for public lectures on cervical cancer. GD declares that her institution (University of Pretoria) received payments (direct and indirect costs) for including patients into the current trial as well as payments for travel for the purpose of meetings. TS declares to have received institutional grants, travel support and honorarium for lectures and articles written for the GlaxoSmithKline group of companies and other pharmaceutical companies; TS is also part of the HPV advisory board. LS declares to have received institutional grant. EW declares to have received payment from GlaxoSmithKline group of companies towards administrative and laboratory fees and travel support for this study. He also declares to have received payments for a cervical cancer advocacy project and for conducting a training program. AM declares to have received payment from GlaxoSmithKline group of companies for laboratory and consultancy services related to clinical trials and epidemiological studies and also payments for associated travel. MM, WQ declare to have no conflict of interest. GR and JS are employees of GlaxoSmithKline group of companies.

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Tables

Table 1. Overview of cases included and demographics of women with invasive cervical cancer

	Ghana	Nigeria	South Africa	Total
Total cases enrolled, N[a]	**167**	**192**	**300**	**659**
Histologically-confirmed, n (%)[b]	**163 (97.6)**	**179 (93.2)**	**228 (76.0)**	**570 (86.5)**
Tumor type[c], n (%)[b]				
SCC	140 (85.9)	147 (82.1)	189 (82.9)	476 (83.5)
ADC	15 (9.2)	12 (6.7)	16 (7.0)	43 (7.5)
ASC	3 (1.8)	2 (1.1)	4 (1.8)	9 (1.6)
MIC	2 (1.2)	0 (0.0)	5 (2.2)	7 (1.2)
OIN	0 (0.0)	3 (1.7)	0 (0.0)	3 (0.5)
UDC	3 (1.8)	2 (1.1)	8 (3.5)	13 (2.3)
Not identifiable[d]	0 (0)	13 (7.3)	6 (2.6)	19 (3.3)
Median age (Min-Max), years				
ICC[e]	56 (25–96)	58 (27–102)	51 (29–85)	55 (25–102)
SCC	57 (27–85)	58 (30–102)	51 (29–85)	54 (27–102)
ADC	56 (25–96)	53 (30–78)	57 (37–84)	56 (25–96)
Mean age ± SD, years				
ICC[e]	58 ± 15	57 ± 15	52 ± 12	55 ± 14
SCC	58 ± 14	58 ± 15	51 ± 12	55 ± 14
ADC	58 ± 19	52 ± 15	57 ± 14	56 ± 16
Ethnic background, %				
African	163 (100)	179 (100)	184 (80.7)	526 (92.3)
White	–	–	4 (1.8)	4 (0.7)
Asian	–	–	1 (0.4)	1 (0.2)
Other	–	–	39 (17.1)	39 (6.8)
HIV status, n (%)[b]				
Positive	3 (1.8)	9 (5.0)	56 (24.6)	68 (11.9)
Negative	2 (1.2)	23 (12.8)	147 (64.5)	172 (30.2)
Unknown	158 (96.9)	147 (82.1)	25 (11.0)	330 (57.9)

[a]N= total number of women with ICC;

[b]n (%)= number (percentage) of women in the specified category

[c]tumor type includes squamous cell carcinoma (SCC), adenocarcinoma (ADC), adenosquamous carcinoma (ASC), microinvasive squamous carcinoma (MIC), other invasive neoplasm (OIN) and undifferentiated carcinoma (UDC)

[d]Samples for which specific histological diagnosis could not be identified at the central laboratory

[e]ICC= invasive cervical cancer

Table 2. Distribution of FIGO cancer stage by age group, tumor type, and HIV status (histologically confirmed cohort)

Categories	IA1	IB	IB1	IB2	IIA	IIB	IIIA	IIIB	IVA	IVB	Missing
Overall (N=570)[a], n (%)[b]	1 (0.2)	12 (2.1)	9 (1.6)	29 (5.1)	52 (9.1)	173 (30.4)	63 (11.1)	192 (33.7)	25 (4.4)	13 (2.3)	1 (-)
Country, n (%)[b]											
Ghana (N=163)	0 (0.0)	4 (2.5)	5 (3.1)	17 (10.4)	20 (12.3)	52 (31.9)	14 (8.6)	45 (27.6)	5 (3.1)	1 (0.6)	-
Nigeria (N=179)	1 (0.6)	8 (4.5)	3 (1.7)	4 (2.2)	25 (14.0)	57 (31.8)	47 (26.3)	29 (16.2)	3 (1.7)	2 (1.1)	-
South Africa (N=228)	0 (0.0)	0 (0.0)	1 (0.4)	8 (3.5)	7 (3.1)	64 (28.1)	2 (0.9)	118 (51.8)	17 (7.5)	10 (4.4)	1 (-)
Age group, n (%)[b]											
≤30 years (N=10)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	3 (30.0)	2 (20.0)	1 (10.0)	3 (30.0)	0 (0.0)	0 (0.0)	-
31–39 years (N=75)	0 (0.0)	1 (1.3)	1 (1.3)	8 (10.7)	9 (12.0)	20 (26.7)	3 (4.0)	27 (36.0)	4 (5.3)	2 (2.7)	-
40–49 years (N=129)	0 (0.0)	5 (3.9)	1 (0.8)	4 (3.1)	11 (8.5)	44 (34.1)	11 (8.5)	42 (32.6)	7 (5.4)	3 (2.3)	1 (-)
50–59 years (N=140)	1 (0.7)	3 (2.1)	3 (2.1)	5 (3.6)	14 (10.0)	51 (36.4)	12 (8.6)	44 (31.4)	5 (3.6)	2 (1.4)	-
60–69 years (N=113)	0 (0.0)	1 (0.9)	1 (0.9)	7 (6.2)	7 (6.2)	29 (25.7)	16 (14.2)	41 (36.3)	8 (7.1)	3 (2.7)	-
≥70 years (N=101)	0 (0.0)	2 (2.0)	3 (3.0)	4 (4.0)	8 (7.9)	26 (25.7)	20 (19.8)	34 (33.7)	1 (1.0)	3 (3.0)	-
Missing (N=2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	-
Tumor type, n (%)[b]											
SCC[c] (N=476)	1 (0.2)	11 (2.3)	6 (1.3)	26 (5.5)	41 (8.6)	133 (27.9)	57 (12.0)	168 (35.3)	23 (4.8)	10 (2.1)	-
ADC[d] (N=43)	0 (0.0)	1 (2.3)	1 (2.3)	1 (2.3)	7 (16.3)	17 (39.5)	3 (7.0)	10 (23.3)	1 (2.3)	2 (4.7)	-
Other (N=32)	0 (0.0)	0 (0.0)	2 (6.3)	2 (6.3)	2 (6.3)	13 (40.6)	1 (3.1)	10 (31.3)	1 (3.1)	1 (3.1)	-
Not Identifiable (N=19)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.5)	10 (52.6)	2 (10.5)	4 (21.1)	0 (0.0)	0 (0.0)	1 (-)
HIV status, n (%)[b]											
Positive (N=68)	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.4)	5 (7.4)	16 (23.5)	0 (0.0)	32 (47.1)	9 (13.2)	3 (4.4)	-
Negative (N=172)	0 (0.0)	1 (0.6)	2 (1.2)	5 (2.9)	11 (6.4)	50 (29.1)	9 (5.2)	78 (45.3)	9 (5.2)	6 (3.5)	1 (-)
Unknown (N=330)	1 (0.3)	11 (3.3)	7 (2.1)	21 (6.4)	36 (10.9)	107 (32.4)	54 (16.4)	82 (24.8)	7 (2.1)	4 (1.2)	-

[a]N= total number of women;

[b]n (%)= number (percentage) of women in the specified category

[c]SCC= squamous cell carcinoma

[d]ADC= adenocarcinoma

Table 3. Distribution of HPV types (% [95% confidence interval]) among women with invasive cervical cancer infected with a single HPV type (HPV-positive cohort)

HPV type[b]	Ghana (N[a]=121)	Nigeria (N[a]=145)	South Africa (N[a]=181)	Total (N[a]=447)
HPV16	55.4 [46.1, 64.4]	52.4 [44.0, 60.8]	47.5 [40.1, 55.1]	51.2 [46.5, 56.0]
HPV18	19.0 [12.4, 27.1]	14.5 [9.2, 21.3]	18.2 [12.9, 24.6]	17.2 [13.8, 21.1]
HPV35	6.6 [2.9, 12.6]	9.0 [4.9, 14.8]	9.9 [6.0, 15.3]	8.7 [6.3, 11.7]
HPV45	6.6 [2.9, 12.6]	7.6 [3.8, 13.2]	7.7 [4.3, 12.6]	7.4 [5.1, 10.2]
HPV33	3.3 [0.9, 8.2]	1.4 [0.2, 4.9]	6.6 [3.5, 11.3]	4.0 [2.4, 6.3]
HPV52	2.5 [0.5, 7.1]	2.8 [0.8, 6.9]	1.7 [0.3, 4.8]	2.2 [1.1, 4.1]
HPV51	1.7 [0.2, 5.8]	2.8 [0.8, 6.9]	1.1 [0.1, 3.9]	1.8 [0.8, 3.5]
HPV31	0.8 [0.0, 4.5]	2.1 [0.4, 5.9]	1.7 [0.3, 4.8]	1.6 [0.6, 3.2]
HPV68/73	0.8 [0.0, 4.5]	0.0 [0.0, 2.5]	2.8 [0.9, 6.3]	1.3 [0.5, 2.9]
HPV56	1.7 [0.2, 5.8]	0.7 [0.0, 3.8]	1.1 [0.1, 3.9]	1.1 [0.4, 2.6]
HPV59	0.0 [0.0, 3.0]	2.8 [0.8, 6.9]	0.6 [0.0, 3.0]	1.1 [0.4, 2.6]
HPV39	0.8 [0.0, 4.5]	1.4 [0.2, 4.9]	0.6 [0.0, 3.0]	0.9 [0.2, 2.3]
HPV58	0.8 [0.0, 4.5]	1.4 [0.2, 4.9]	0.0 [0.0, 2.0]	0.7 [0.1, 1.9]
HPV53	0.0 [0.0, 3.0]	0.7 [0.0, 3.8]	0.0 [0.0, 2.0]	0.2 [0.0, 1.2]
HPV66	0.0 [0.0, 3.0]	0.0 [0.0, 2.5]	0.6 [0.0, 3.0]	0.2 [0.0, 1.2]
HPV70	0.0 [0.0, 3.0]	0.7 [0.0, 3.8]	0.0 [0.0, 2.0]	0.2 [0.0, 1.2]

[a]N= total number of women infected with a single HPV type

[b]In 11 HPV positive women, the HPV type could not be determined.

Table 4. Distribution of HPV types (% [95% confidence interval]) according to tumor type in women with invasive cervical cancer infected with a single HPV type (HPV-positive cohort)

HPV type	Single ICC[b] (N[a]=447)	SCC[c] (N[a]=394)	ADC[d] (N[a]=27)
HPV16	51.2 [46.5, 56.0]	53.8 [48.7, 58.8]	22.2 [8.6, 42.3]
HPV18	17.2 [13.8, 21.1]	15.0 [11.6, 18.9]	29.6 [13.8, 50.2]
HPV35	8.7 [6.3, 11.7]	9.4 [6.7, 12.7]	3.7 [0.1, 19.0]
HPV45	7.4 [5.1, 10.2]	7.1 [4.8, 10.1]	18.5 [6.3, 38.1]
HPV33	4.0 [2.4, 6.3]	3.8 [2.1, 6.2]	3.7 [0.1, 19.0]
HPV52	2.2 [1.1, 4.1]	2.3 [1.0, 4.3]	-
HPV51	1.8 [0.8, 3.5]	2.0 [0.9, 4.0]	-
HPV31	1.6 [0.6, 3.2]	1.5 [0.6, 3.3]	3.7 [0.1, 19.0]
HPV68/73	1.3 [0.5, 2.9]	1.3 [0.4, 2.9]	3.7 [0.1, 19.0]
HPV56	1.1 [0.4, 2.6]	0.8 [0.2, 2.2]	7.4 [0.9, 24.3]
HPV59	1.1 [0.4, 2.6]	0.8 [0.2, 2.2]	7.4 [0.9, 24.3]
HPV39	0.9 [0.2, 2.3]	1.0 [0.3, 2.6]	-
HPV58	0.7 [0.1, 1.9]	0.5 [0.1, 1.8]	-
HPV53	0.2 [0.0, 1.2]	0.3 [0.0, 1.4]	-
HPV66	0.2 [0.0, 1.2]	0.3 [0.0, 1.4]	-
HPV70	0.2 [0.0, 1.2]	0.3 [0.0, 1.4]	-

[a]N= total number of women infected with a single HPV type

[b]ICC= invasive cervical cancer

[c]SCC= squamous cell carcinoma

[d]ADC= adenocarcinoma

Table 5. Distribution of HPV types (% [95% confidence interval]) according to HIV status in women with invasive cervical cancer infected with a single HPV type (HPV-positive cohort)

HPV type	HIV positive (N[a]=55)	HIV negative (N[a]=140)	Unknown HIV status (N[a]=252)
HPV16	49.1 [35.4, 62.9]	51.4 [42.8, 60.0]	51.6 [45.2, 57.9]
HPV18	27.3 [16.1, 41.0]	15.0 [9.5, 22.0]	16.3 [11.9, 21.4]
HPV35	7.3 [2.0, 17.6]	8.6 [4.5, 14.5]	9.1 [5.9, 13.4]
HPV45	7.3 [2.0, 17.6]	8.6 [4.5, 14.5]	6.7 [4.0, 10.6]
HPV33	-	7.1 [3.5, 12.7]	3.2 [1.4, 6.2]
HPV52	1.8 [0.0, 9.7]	1.4 [0.2, 5.1]	2.8 [1.1, 5.6]
HPV51	-	1.4 [0.2, 5.1]	2.4 [0.9, 5.1]
HPV31	3.6 [0.4, 12.5]	1.4 [0.2, 5.1]	1.2 [0.2, 3.4]
HPV68/73	1.8 [0.0, 9.7]	1.4 [0.2, 5.1]	1.2 [0.2, 3.4]
HPV56	-	1.4 [0.2, 5.1]	1.2 [0.2, 3.4]
HPV59	-	2.1 [0.4, 6.1]	0.8 [0.1, 2.8]
HPV39	-	-	1.6 [0.4, 4.0]
HPV58	-	-	1.2 [0.2, 3.4]
HPV53	-	-	0.4 [0.0, 2.2]
HPV66	1.8 [0.0, 9.7]	-	-
HPV70	-	-	0.4 [0.0, 2.2]

[a]N= total number of women infected with a single HPV type

Table 6. Distribution of HPV types (% [95% confidence interval]) among women with invasive cervical cancer infected with multiple HPV types (HPV-positive cohort)

HPV type	Ghana (N^a=29)	Nigeria (N^a=6)	South Africa (N^a=22)	Total (N^a=57)
HPV16	72.4 [52.8, 87.3]	50.0 [11.8, 88.2]	36.4 [17.2, 59.3]	56.1 [42.4, 69.3]
HPV18	41.4 [23.5, 61.1]	50.0 [11.8, 88.2]	31.8 [13.9, 54.9]	38.6 [26.0, 52.4]
HPV45	20.7 [8.0, 39.7]	50.0 [11.8, 88.2]	45.5 [24.4, 67.8]	33.3 [21.4, 47.1]
HPV52	31.0 [15.3, 50.8]	33.3 [4.3, 77.7]	9.1 [1.1, 29.2]	22.8 [12.7, 35.8]
HPV35	24.1 [10.3, 43.5]	33.3 [4.3, 77.7]	9.1 [1.1, 29.2]	19.3 [10.0, 31.9]
HPV33	13.8 [3.9, 31.7]	0.0 [0.0, 45.9]	18.2 [5.2, 40.3]	14.0 [6.3, 25.8]
HPV31	3.4 [0.1, 17.8]	0.0 [0.0, 45.9]	9.1 [1.1, 29.2]	5.3 [1.1, 14.6]
HPV51	3.4 [0.1, 17.8]	0.0 [0.0, 45.9]	9.1 [1.1, 29.2]	5.3 [1.1, 14.6]
HPV11	0.0 [0.0, 11.9]	0.0 [0.0, 45.9]	9.1 [1.1, 29.2]	3.5 [0.4, 12.1]
HPV54	0.0 [0.0, 11.9]	16.7 [0.4, 64.1]	4.5 [0.1, 22.8]	3.5 [0.4, 12.1]
HPV58	0.0 [0.0, 11.9]	16.7 [0.4, 64.1]	4.5 [0.1, 22.8]	3.5 [0.4, 12.1]
HPV68/73	0.0 [0.0, 11.9]	0.0 [0.0, 45.9]	9.1 [1.1, 29.2]	3.5 [0.4, 12.1]
HPV6	0.0 [0.0, 11.9]	0.0 [0.0, 45.9]	4.5 [0.1, 22.8]	1.8 [0.0, 9.4]
HPV44	0.0 [0.0, 11.9]	0.0 [0.0, 45.9]	4.5 [0.1, 22.8]	1.8 [0.0, 9.4]
HPV56	3.4 [0.1, 17.8]	0.0 [0.0, 45.9]	0.0 [0.0, 15.4]	1.8 [0.0, 9.4]
HPV59	0.0 [0.0, 11.9]	0.0 [0.0, 45.9]	4.5 [0.1, 22.8]	1.8 [0.0, 9.4]
HPV66	0.0 [0.0, 11.9]	0.0 [0.0, 45.9]	4.5 [0.1, 22.8]	1.8 [0.0, 9.4]
HPV74	0.0 [0.0, 11.9]	0.0 [0.0, 45.9]	4.5 [0.1, 22.8]	1.8 [0.0, 9.4]

[a]N= total number of women infected with multiple HPV types