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Prevalence and Type Distribution of Human Papillomavirus in Invasive Cervical Cancer in Aba, South-East Nigeria: A Sentinel Study to Encourage and Guide HPV Vaccination

Akwuruoha Emmanuel	Department of Obstetrics and Gynaecology, Abia State University Teaching Hospital, Aba, Abia State, Nigeria.
Onwuka Chidi	Department of Histopathology, University of Uyo Teaching Hospital, Uyo, Akwa Ibom State, Nigeria.
Eleweke Ndukauba	Department of Surgery, Faculty of Clinical Sciences, Abia State University Teaching Hospital, Aba, Abia State, Nigeria.
Umezurike Chisara	Department of Obstetrics and Gynaecology, Rhema University Teaching Hospital, Aba, Abia State, Nigeria.
Kamanu Chuks	Department of Obstetrics and Gynaecology, Abia State University Teaching Hospital, Aba, Abia State, Nigeria.
Eleweke Chimdi	Department of Surgery, Faculty of Clinical Sciences, Abia State University Teaching Hospital, Aba, Abia State, Nigeria.

Background: Despite the established link between human papillomavirus (HPV) and the pathogenesis of invasive cervical cancer and its precursor lesions, HPV vaccine acceptance faces cultural and religious biases in this region. There is no available local epidemiological study to support the current advocacy of HPV vaccination for the primary prevention of cervical cancer in this region. In this cross-sectional epidemiological study, we determined the prevalence and types of HPV in invasive cervical cancer so as to encourage and guide HPV vaccination for the primary prevention of cervical cancer in this south-east region of Nigeria.

Methology: Two-hundred archived formalin-fixed, paraffin-embedded tissue blocks with confirmed diagnoses of invasive cervical cancer during the study period (2015-2024) were retrieved and examined. DNA was extracted by proteinase k lysis procedure while HPV DNA amplification, detection and typing was done using E7 type-specific multiplex genotyping (E7-MPG), which combines multiplex polymerase chain reaction (PCR) and hybridization to type-specific oligonucleotide probes on fluorescent beads.

Result: Fourteen blocks were excluded from the analysis for inadequacy. A total of 79% (147/186) invasive cervical cancers were positive for single or multiple high-risk HPV types. HPV 16 was the predominant high risk HPV-type, being present in 87.3% of the cases in single and multiple infections. The five most common high risk HPV types seen in single infections are HPV 16 (31.3%), HPV 18 (19.7%), HPV 35 (5.4%), HPV 31 (1.4%) and HPV 52 (1.4 %).

Conclusion: There is high prevalence of HPV-DNA in invasive cervical cancers in this region, with HPV 16, HPV 18, HPV 35, HPV 31, and HPV 52 being the predominant types. HPV vaccination and testing will greatly reduce the burden of cervical cancer in this geographical region.

Introduction

Cervical cancer is the commonest cancer of the female genital tract in Nigeria and the second most common cancer in women worldwide [1, 2]. It is a major cause of cancer-related morbidity and mortality in women in developing countries [3, 4]. It is estimated that 15 out of every 1000 women in developing countries will develop cervical cancer before the age of 65 years [5].

Persistent infection with certain types of human papilloma virus (HPV) is the major etiologic factor in the development of cervical cancer and its precursor lesions [6]. There are over 200 genotypes of HPV classified into high and low risk types [7]. About 40 types can infect the uterine cervix of which types 16, 18, 31, 33, 35, 39, 45, 51,

52, 56, 58, 59 and 66 are classified as group 1 carcinogens [7]. Types 16 and 18 are the commonest worldwide and have been associated with more than 70 % of invasive cervical cancer (ICC) [7, 8]. Some HPV types tend to be transmitted together causing concurrent infections with different HPV types in some ICC [7].

The high prevalence of HPV DNA in cervical cancers and its precursor lesions has led to the advocacy for a widespread population-based HPV vaccination to prevent cervical cancers. The great reduction in the incidence of cervical cancer in developed nations has been attributed to organised screening programmes and prophylactic HPV vaccination. But there are concerns that there is regional variation in the distribution of HPV types and the proportion of cervical cancer preventable by HPV vaccine might be lower in sub-saharan africa [9]. Also, vaccine implementation in Nigeria has met with barriers including religious and cultural biases. This study aims to determine the prevalence and type of HPV DNA associated with cervical cancer in this region. To the best of our knowledge, this is a sentinel study in this state and will provide a local epidemiological data to encourage and guide the implementation of HPV vaccination for the primary prevention of cervical cancer in this region.

Materials and Methods

Study design and ethical considerations

This cross-sectional, point prevalence, hospital-based epidemiological study was carried out in Abia state university teaching hospital (ABSUTH), Aba, Abia state, south-east geopolitical zone of Nigeria. The pathology department of the hospital serves patients of ABSUTH and other private hospitals in Aba. The study was approved by the institutional health ethical research committee (IHERC) of ABSUTH in line with the declaration of helsinki and good clinical practice guidelines.

Study Specimen

The study specimens are biopsies of the uterine cervix in paraffin blocks. Two hundred, archival, formalin-fixed, paraffin-embedded (FFPE) tissue blocks of cervical cancer cases diagnosed between August 2015 and May 2024 were randomly retrieved for the study. Patient information was retrieved from the original request forms. The original biopsy specimens were obtained by a gynecologist from women who presented with cervical lesions suspicious of invasive cervical cancer at ABSUTH and other private hospitals in Aba as part of routine investigative procedures. The wet specimens were immediately fixed in 10% buffered formalin and processed for paraffin wax embedding using standard protocol. The histologic diagnosis of invasive cervical cancer was determined by light microscopic examination of hematoxylin and eosin (H/E) stained sections. The tissue blocks were stored at room temperature.

Parafin sections for tumour evaluation

To confirm the initial diagnosis and classify the tumour in line with WHO classification, fresh sections were taken from the tissue blocks for light microscopic examination of H/E stained sections. Two hundred suitable blocks with confirmed diagnosis of invasive cervical cancer were used for the HPV DNA detection and typing.

Parafin Sections for DNA Extraction

Three 10-mm, thick sections were taken from each block and put in a 1.5 ml safe-lock, sterile, eppendorf tube (Germany) with the aid of millipore tweezers. To prevent cross-contamination between specimens, the microtome and microtome blade were extensively cleaned after sectioning each block with a gauze soaked in DNA cleaner (DNA away, molecular bioproducts, ref: 7010) followed by 70 percent ethanol. The tubes containing the tissue sections were shipped to IARC lab (Lyon, France) for DNA extraction and typing.

DNA Extraction

DNA was extracted by overnight incubation of the paraffin tissue sections in 250 µl of digestion buffer (10 mm Tris/Hcl at ph 7.4, 0.5 mg/ml proteinase k, and 0.4% tween 20) at 37℃. To inactivate proteinase k and to separate paraffin from the aqueous phase, samples were incubated at 95 °C for 10 min, centrifuged, and chilled on ice. The aqueous phase is then transferred to a new tube. The solution is purified by the use of a high pure PCR template preparation kit (roche, basel, switzerland), according to the manufacturer’s instructions. The DNA is eluted in 0.2 ml of elution buffer (10 mm tris, ph 8.5) and stored at −20°C until further use.

Amplification and DNA typing

HPV-DNA positivity was determined using a type- specific multiplex genotyping (E7-MPG) assay, which combines multiplex PCR and bead-based luminex technology (luminex corporation, Austin, TX) [10]. This assay detects twelve HR-HPVs (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59), seven probable HR (pHR)-HPVs (HPV26, 53, 66, 68, 70, 73, 82), and two low-risk (LR) HPVs (HPV6 and 11), as well as cellular beta-globin gene which is used to for DNA quality. The PCRs were performed with the QIAGEN multiplex pcr kit according to the instructions of the manufacturer. After PCR amplification (TS-PCR), 10 µl of each reaction mixture was analysed by multiplex HPV genotyping (MPG) using luminex technology (luminex corporation, Austin, TX).

Data Analysis

The data collated were analysed using statistical package for social sciences version 20 (spss 20) and the results presented as Tables and charts. Statistical comparison was done using chi-square with the level of significance set at p less or equal to 0.05. The findings of this study were compared with those of previous studies.

Results

Descriptive Data

Two hundred invasive cervical cancer cases seen between august 2015 and may 2024 were used for

the study. Out of the 200 cases, 14 cases were excluded from the analysis since they were β-globin negative. The patients were aged from 23 to 86 years. majority of the patients were above 50 years; the mean age was 54.54 (SD 12.87).

Types of cervical cancer

Majority of the cervical cancers seen in this study were squamous cell carcinoma and its variants (80.10%), followed by adenocarcinoma and its variants (14 %). adenosquamous carcinoma, carcinosarcoma and sarcomas make up less than 6% of the cervical cancer types seen.

Prevalence and

Out of the 186 cases used for statistical analysis, 147 cases (79%) were positive for HPV-specific DNA. Nine [9] different high-risk HPV genotypes were detected (Table 1).

HPV	Negative	Positive (%)	95%CI
HPV11	180 (96.8)	6 (3.2)	1.4 - 6.5
HPV16	87 (46.8)	99 (53.2)	46.1 - 60.3
HPV18	116 (62.4)	70 (37.6)	30.9 - 44.7
HPV31	181 (97.3)	5 (2.7)	1.0 - 2.5
HPV33	185 (99.5)	1 (0.5)	0.1 - 2.5
HPV35	161 (86.6)	25 (13.4)	9.1 - 18.9
HPV45	183 (97.8)	3 (1.6)	0.5 - 4.2
HPV51	182 (97.8)	4 (2.2)	0.7 - 5.0
HPV52	182 (97.8)	4 (2.2)	0.7 - 5.0
HPV82	183 (98.4)	3 (1.6)	0.5 - 4.2

Table 1. Specific HPV Strain Prevalence. Nine high-risk HPV genotypes were detected, HPV16 being the most common (53.2% of cases).

They included HPV 16, HPV 18, HPV 31, HPV 33, HPV 35, HPV 45, HPV 51, HPV 52, and HPV 82. HPV 16 is the most common genotype detected (53.2% of cases), followed by HPV 18 (37.6%). Less common high-risk genotypes seen include HPV 31 and HPV 33. This highlights the dominance of high-risk HPV strains, particularly HPV 16 and HPV 18.

Single and multiple high-risk HPV co-infections were observed (Table 2).

HPV Genotype	Frequency (n)	Percent (%)
HPV16	46	31.3
HPV18	29	19.73
HPV 16 &18	28	19.05
HPV 35	8	5.44
HPV 16, 18 & 35	5	3.4
HPV 16 & 35	5	3.4
HPV16 & 31	2	1.36
HPV18 & 35	2	1.36
HPV 31	2	1.36
HPV 52	2	1.36
HPV11,16 & 18	2	1.36
HPV11 & 16	1	0.68
HPV11,16,18 & 35	1	0.68

HPV 11,16,35 & 45	1	0.68
HPV11 & 18	1	0.68
HPV16,18 & 52	1	0.68
HPV16,35 & 45	1	0.68
HPV16,35 & 51	1	0.68
HPV16, 35 & 82	1	0.68
HPV16,18 & 51	1	0.68
HPV16 & 31	1	0.68
HPV16 & 51	1	0.68
HPV16 & 82	1	0.68
HPV 33	1	0.68
HPV 45	1	0.68
HPV 51 & 52	1	0.68
HPV 82	1	0.68
Total	147	100

Table 2. Frequency of Single and Multiple HPV Infections. There were 90 (48.4%) cases of single HPV infection and 96 (51.6%) cases of multiple HPV infections. HPV16 and HPV18 accounted for 90.8%.

There were 90 (48.4%) cases of single HPV infection and 96 (51.6%) cases of multiple HPV infections. A co-infection with low-risk HPV 11 was seen in five cases (4.08%). In both single and multiple HPV infections, the three most frequent high-risk HPV genotypes detected were HPV 16 (53.2%), HPV 18 (37.6%) and HPV 35 (13.4%). HPV 16 and HPV 18 accounted for 90.8%. In multiple HPV infections, double infections with HPV 16 and 18 was the most frequent, observed in 28 (19.05%) cases. Triple and quadruple HPV infections were also seen.

When we considered the type of cervical cancer, the highest HPV positivity was seen in squamous cell carcinoma (Figure 1).

Figure 1. Shows the Relationship between HPV Positivity and the Type of Cervical Cancer Seen in This Study. The highest positivity is observed in Squamous cell carcinoma (83.9%), with significant variability among other types, reflected in a p-value of 0.007. SQC=Squamous cell carcinoma; ADC=Adenocarcinoma; ASC=Adenosquamous carcinoma; CSA=Carcinosarcoma; SAR=Sarcoma.

Considering the HPV positivity across the age groups used in this study shows that HPV 16 is consistently dominant across all age groups (Figure 2).

Figure 2. Examines HPV Strain Distribution by Age Group, with HPV16 Being Consistently Dominant Across all Age Categories. There is no significant differences in strain distribution across ages suggesting that the prevalence of specific HPV types remains steady, regardless of age. This points to widespread exposure across the lifespan.

Discussion

It has been established that infection with high-risk HPV is the most important aetiologic agent in the pathogenesis of cervical cancer [6, 7]. Determining the HPV type distribution in cervical cancers in different geographical regions is an essential step in the development of population-specific prophylactic HPV vaccine strategies. Several studies have led to the advocacy for prophylactic HPV vaccines against the development of HPV-associated cervical pre-malignant lesions [11]. Despite the fact that cervical cancer is the commonest gynaelogical cancer in Nigeria and contribute significantly to cancer related deaths in women [2], only few studies have been conducted in this country to determine the prevalence and type distribution of HPV in cervical

cancer [12-16]. To the best of our knowledge, no such study has been done in this state. In addition, from our experience, HPV vaccine reception in this part of the world has religious and cultural sentiments as barriers. To encourage and guide HPV vaccination for the primary prevention of cervical cancer in this region, we have determined the HPV prevalence and type distribution in cervical cancer in this South-East region of Nigeria.

Worldwide, there are geographical variations in the prevalence and type distribution of HPV-DNA in cervical cancers [11]. The overall prevalence has been reported to be in the range of 90-100% [17, 18]. In this study, HPV positivity in squamous cell carcinoma is 83.9%. A total prevalence of 79% was recorded when all the cancer types were considered. This result is comparable to results obtained in other studies conducted in Nigeria [15, 16], Ethiopia [19], and Serbia [20]. Some studies have reported prevalence rates of greater than 90%. These includes studies carried out in Nigeria [12, 21], Ghana [22], Malawi [23], South Africa [12], India [24], and USA [25]. Also, relatively low HPV-DNA prevalence rates have been observed in cervical cancer in studies done in iran [26] and poland [27]. These differences in the prevalence rates of HPV-DNA in cervical cancers have been attributed to geographical variations [28], quantity and quality of the tissue specimen [22], method of DNA extraction and sensitivity of the method [29], the specificity of the detection method [30] and type of cervical cancer studied. HPV infects mucosal surfaces [7]. This can explain why studies using only squamous cell carcinomas (the commonest type of cervical cancer) obtained higher prevalences as seen in some of the studies mentioned above. in this study, HPV positivity was seen in 125/149 (83.9%) of squamous cell carcinomas.

The spectrum of HPV-DNA detected in cervical cancers also show regional variations. All over the world, HPV-16 and -18 are the predominant HR-HPV types detected [12]. In this study, eight different high-risk (HPVs-16, 18, 31, 33, 35, 45, 51, and 52) and one

probable high-risk (HPV-82) hpv types were identified. A co-infection with low-risk HPV 11 was observed in five cases. Both single and multiple HPV infections were observed. The three most prevalent high-risk HPV genotypes in this study in decreasing order of frequency were HPV 16, HPV 18, HPV 35. HPV 16 and HPV 18 accounted for 40.3% and 70% of single and multiple infections, respectively. This finding is consistent with several studies across the world [12, 15, 24, 25]. The high prevalence of multiple infections has been attributed to factors like multiple sexual partners and immunosuppression [21], and may be explained by the fact that prior infection with one HPV-type does not decrease the risk of infection by another HPV-type and supports the use of multivalent vaccines [31]. There is conflicting evidence on the significance of multiple infections. Some studies have shown that infection with multiple HPV-types exhibit synergism and additivity of effect and are associated with persistence of infection, increased risk of disease progression, disease severity and poorer outcomes [32, 33]. This is contrary to the findings by salazar et al [34] which shows a reduced rate of high-grade cervical lesions in multiple infections due to intergenotypic competition and/or effective immune response.

Despite the recognition of geographical variation in the prevalence of HPV types [35], HPV-16 and HPV-18 are the most prevalent and the most potent carcinogenic viruses with a higher probability of persistence and disease progression [6, 34]. The four major stages in cervical cancer pathogenesis includes infection of a metaplastic epithelium at the transformation zone, high-risk HPV viral persistence, progression of the persistently infected epithelium to precancer, and invasion of the basement membrane of the epithelium [7].

Because prior infection with one HPV-type does not decrease the risk of infection by another HPV-type [31], multivalent HPV vaccines hold great promise to reduce the burden of ICC globally. It can be deduced from this study that the currently available bivalent (against HPV 16 and HPV 18), quadrivalent (against HPV 6, HPV 11, HPV 16 and HPV 18), and nonavalent (against HPV 6, HPV 11, HPV 16, HPV 18, HPV 31, HPV 33, HPV 45, HPV 52 and HPV 58) HPV vaccines can prevent majority of the HPV infections in this environment. This is because in this study, the combined proportions of positivity for HPV 16, HPV 18, HPV 31, HPV 33, HPV 45, HPV 52 and HPV 11 is

greater than 80%. Reducing the incidence of hpv infections will also protect unvaccinated individuals through herd immunity [14]. Also, because Pap test has relatively high specificity but low sensitivity in detecting HPV infections [36], introducing HPV DNA testing as part of the protocol for cervical cancer screening will improve the sensitivity of Pap test for cervical cancer screening in women above 30 years in this region.

In conclusion, there is high prevalence of HPV-DNA in invasive cervical cancers in this region, with HPV 16, HPV 18, HPV 35, HPV 31, and HPV 52 being the predominant types. This observed high prevalence of HPV in invasive cervical cancers and the predominance of HPV 16 and HPV 18 is a worldwide phenomenon consistent with several studies. The high proportion of multiple HPV types detected in the samples supports multiple sexual partners as a risk factor for cervical cancer in this environment. Being a sentinel study in this state, the findings of this study will serve as baseline data. HPV vaccination and testing will greatly reduce the burden of cervical cancer in this geographical region. The currently available HPV vaccines will be beneficial in this region.

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Conflict of Interest

None

Ethical declaration

The study was approved by the institutional health ethical research committee (IHERC) of absuth in line with the declaration of helsinki and good clinical practice guidelines.

Authors contribution

AE and OC conceived the study. all authors were involved in the conduct of the study. OC and UC were involved in drafting the manuscript. all authors read and approved the final version of the manuscript.

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