

## Prevalence and Risk Factors of Human Papilloma Virus Infection among Women in a Nigerian State

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Received: August 05, 2019; Published: August 19, 2019

### Abstract

Human Papilloma Virus (HPV) infection is the primary cause of virtually all cervical cancers. Although most HPV infections are subclinical and self-limiting within 1 - 2 years, the infection persists in about 5 - 10% of infected women, resulting to pre-cancerous lesions which can progress to invasive cancer, 15 - 20 years later. This cross-sectional study was carried out to determine the prevalence of HPVs among women attending some hospitals in Kaduna State, Nigeria. The study combined the use of questionnaire to obtain data on socio-demographic and risk factors as well as the analysis of cervical scrapings samples obtained from 276 consenting women. The samples were analyzed for HPV antigen using Enzyme-Linked Immuno Sorbent Assay. A prevalence rate of 8.7% (24/276) for HPV was obtained. Socio-demographic factors associated with HPV infection were age, marriage type and level of education ( $P \leq 0.05$ ) while marital status, occupation and ethnic group were not associated with HPV infection ( $P > 0.05$ ). The risk factors that were found to predispose to HPV infection were multiple sexual partners and high parity. The prevalence rate obtained for HPV in this study is appreciable, which implies that HPV is actively circulating in the region and therefore emphasizes the need for the Government to make sufficiently available, vaccines for HPV in the study area.

**Keywords:** Prevalence; Risk Factors; Human Papilloma Virus; ELISA; Kaduna State; Nigeria

### Study Background

Human Papilloma Virus (HPV) is a naked double-stranded DNA virus, belonging to the family *Papillomaviridae* [1]. The virus establishes infection in the keratinocytes of the skin and mucus membrane [1]. Although most of these infections are subclinical, there are instances when subclinical infections will become clinical and may cause benign papilloma or cancers of the genitalia [2].

It is not clearly understood why HPV infections resolve in certain individuals and result in more severe lesions in others. It is however revealed that an individual's susceptibility and other enabling factors such as; immune status, nutrition, endogenous and exogenous hormones, tobacco smoking, high parity, prolonged use of oral contraceptives, genetic disorders, early sexual debut, non-circumcision of the male partner and co-infection with other sexually-transmitted agents such as HIV, Herpes Simplex Virus type 2 (HSV-2) and *Chlamydia trachomatis*, play a role in the development of lesions [3,4].

Cervical cancer is the 2nd most common female cancer in women aged 15 to 44 years in Nigeria, with 14,943 new cases diagnosed and 10,403 deaths occurring annually (estimates for 2018) [5]. This represents loss of 28 women every day.

Human Papilloma Virus infection is the cause of nearly all cases of cervical cancer [6] and there is currently no specific treatment for HPV infection.<sup>2</sup> Although there are vaccines for some high-risk HPV (hrHPV) types, the vaccines has been shown to be of no use in already infected women, it is therefore recommended only for uninfected women.

Some reports on the studies of HPV conducted in different parts of Nigeria have recorded different prevalence rates, ranging from 19.6% - 76%, for Immunoglobulin G antibody to HPV and hrHPV [7-13], thus indicating a high prevalence of this virus. Magaji *et al.* [14] reported the presence of certain hrHPV types in Kaduna State, Nigeria, but an overall prevalence of the virus in the state has not yet been reported. It is in view of this that this work finds relevance. Human Papilloma Virus Infection is a necessary but not sufficient cause of cervical cancer; therefore identifying specific risk factors to the infection in the State is paramount, as this will help in creating awareness on the prevention strategies.

### Materials and Methods

#### Study area and data collection

This was a hospital-based and cross-sectional study that was conducted in different hospitals from the three senatorial zones of Kaduna State, Nigeria. Ethical Approval was obtained from the Kaduna State Ministry of Health before the study commenced. Informed consent was sought from the respondents prior to sample and data collection. Also, Human Experimentation Guidelines as provided by the CPCSEA and World Medical Association Declaration of Helsinki were followed in the conduct of the research. The sample size was calculated based on a prevalence obtained from a previous study conducted in Osun State, Nigeria<sup>9</sup> using the equation derived by Sarmukadam and Garad [15]. Structured questionnaire was used to obtain socio-demographic and clinical data related to HPV from the respondents. Non-consenting women were excluded from the study.

#### Sample collection and processing

Cervical scrapings were collected by a gynecologist, from 276 women, aged 15 years and above, attending the selected hospitals. A sterile cytobrush was used to collect the exfoliated cells from the squamo-columnar junction of the ecto and endo cervix. The cells were then rinsed in 5 ml phosphate buffered saline and stored at -20°C in the laboratory unit of the various hospitals until analyzed. They were transported in iceboxes to the Department of Microbiology, Ahmadu Bello University, Zaria, where they were subjected to Enzyme-Linked Immunosorbent Assay (ELISA).

#### Detection of human papilloma virus

The cervical scrapings samples were analyzed using Human Papilloma Virus Antigen ELISA Kit in Cervical Swab, (WKEA MED SUPPLIES, CHANGCHUN, CHINA) to check for the presence of viral antigen. The ELISA utilizes the ability of HPV antigen to react specifically to purified antibodies coated on the wells of micro titer plate and the eventual detection of this antigen-antibody complex with a secondary antibody conjugated to an enzyme that can react with a chromogenic substrate. The test was done according to the manufacturer's instruction. The cervical cell suspensions were transferred into Eppendorf tubes and centrifuged at 10,000rpm for 5 minutes, after which the supernatant was discarded and the sediment was used for the assay. All reagents were brought to room temperature and mixed thoroughly before use. The cut off value was calculated using the manufacturer's specifications. The average of negative control well plus 0.15 was taken as the cut off value. Any sample whose optical density was higher than the calculated cut off value was reported positive for HPV.

#### Data analysis

The data obtained was analyzed using Statistical Analysis System (SAS) version 9.2 at 0.05 level of significance and 95% confidence interval. Relationships between variables were determined using Fishers Exact Test and the degree of association was determined using Odds Ratio.

## Results

Analysis of the study population by socio-demographic features revealed that more than half (52.9%: 146/276) of the respondents were between ages 37- 56 years and married (78.6%: 217/276). Most were Civil servants (51.4%: 142/276) with a good literacy level (44.6%: 123/276). Concerning their sexual and reproductive characteristics, a good number (47.5%: 131/276) of the respondents were multiparous women that practice monogamy (81.9%: 226/276) and had their first sexual contact after age 20 years (51.4%: 114/276).

Of the 276 cervical scrapings analyzed for HPV, 24 (8.7%) were positive, with most cases (4.0%: 11/276) coming from Kaduna South (Table 1).

Senatorial Zone	Number Screened	Number Positive	Percentage (%)	P-Value
South	92	11	4.0	
Central	92	4	1.4	0.0059
North	92	9	3.3	
Total	276	24	8.7	

**Table 1:** Prevalence of human papilloma virus among women in Kaduna state, Nigeria.

Respondents that were in age group 27 - 36 years had the highest prevalence of HPV (11.9%: 8/67) while those in age group 17 - 26 years had the lowest (3.6%: 1/28) (Table 2). Age was statistically associated with HPV infection ( $\chi^2 = 20.341$ ,  $df = 5$ ,  $P = 0.0062$ ).

Variable	Number Analyzed	Number Positive (%)	P-Value
<b>Age (years)</b>			
17 years - 26 years	28	1 (3.6)	0.0062
27 years - 36 years	67	8 (11.9)	
37 years- 46 years	81	6 (7.4)	
47 years- 56 years	65	6 (9.2)	
57 years - 66 years	26	2 (7.8)	
67 years - 76 years	9	1 (11.1)	
<b>Marital Status</b>			0.0541
Single	14	0 (0.0)	
Married	217	19 (8.8)	
Divorced	3	1 (33.3)	
Widowed	39	3 (7.6)	
Separated	3	1 (33.3)	
<b>Level of Education</b>			0.0001
Primary	53	4 (7.5)	
Secondary	89	12 (13.5)	
Tertiary	123	8 (6.5)	
Informal	2	0 (0.0)	
None	9	0 (0.0)	
<b>Occupation</b>			0.3012
Civil Servant	142	9 (6.3)	
Business	50	6 (12.0)	
Farming	25	3 (12.0)	
Others	59	6 (10.2)	

**Table 2:** Prevalence of human papilloma viruses based on socio-demographic features among women in Kaduna state, Nigeria.

Taking level of education as a factor, it was observed that women that never went beyond secondary school had the highest rate of infection (13.5%: 12/89) and this difference was statistically significant ( $\chi^2 = 10.422$ ,  $df = 5$ ,  $P = 0.0001$ ).

The sexual and reproductive features of the respondents were analyzed as shown in Table 3. Although most of the respondents were in a monogamous marriage, HPV infection was however, higher (13.9%: 5/36) in the few that were in a polygamous marriage ( $\chi^2 = 25.000$ ,  $df = 2$ ,  $P = 0.0001$ ).

Variable	Number Analyzed	Number Positive (%)	P-Value
<b>Type of Marriage</b>			
Monogamy	226	19 (8.4)	0.0001
Polygamy	36	5 (13.9)	
Not Available	14	0 (0.0)	
<b>Age at Sexual Debut (years)</b>			
13 - 16	22	2 (9.1)	0.0641
17 - 20	112	11 (8.8)	
> 20	142	11 (7.7)	
<b>Multiple Sexual Partners</b>			
Yes	75	13 (17.3)	0.0346
No	201	11 (5.5)	
<b>Parity</b>			
Nulliparous	31	1 (3.2)	0.0361
Primiparous	23	2 (8.7)	
Multiparous	131	9 (6.9)	
Grand multiparous	91	12 (13.3)	

**Table 3:** Distribution of human papilloma viruses based on some sexual and reproductive features among women attending some hospitals in Kaduna state.

The respondents that had their sexual debut at age 17 - 20 years had the highest rate of HPV infection (9.8%: 11/112) with no significant difference ( $\chi^2 = 10.551$ ,  $df = 2$ ,  $P = 0.0641$ ). Having multiple sexual partner was defined in the study as having sex with more than one person, therefore it was observed that women with multiple sexual partners had a higher prevalence of 17.3% (13/75) and this difference was statistically significant ( $\chi^2 = 10.112$ ,  $df = 1$ ,  $P = 0.0346$ ,  $OR = 1.399$ ).

Relating parity with HPV infection showed that women that had five or more deliveries (Grand multiparous) had the highest prevalence of 13.2% (12/91), while nulliparous women had the lowest (3.2%: 1/31). Parity was significantly associated with HPV infection in the study with the infection increasing with increase in number of deliveries ( $\chi^2 = 9.505$ ,  $df = 3$ ,  $P = 0.0361$ ).

Some risk factors that predispose to HPV infection were examined (Table 4). The result revealed that HPV infection was most prevalent (10.0%: 3/30) in women that took oral contraceptives for more than 10 years while it was lowest (4.8%: 1/21) and it was detected in only one woman (4.8%) out of the 21 women that have taken contraceptive for 5-10 years. There was no association between HPV infection and the use of oral contraceptives ( $\chi^2 = 14.306$ ,  $df = 3$ ,  $P = 0.3012$ ).

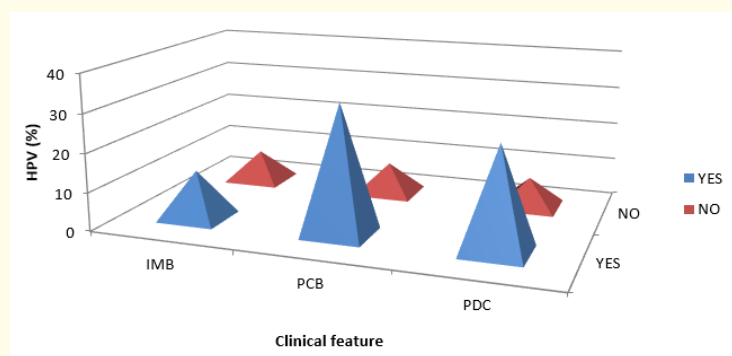
Analysis of the co-infection of HPV and HIV revealed that women that were infected with HIV had a higher prevalence rate (12.5%: 2/16) of HPV infection and there was a statistically significant association between infection with HIV and HPV ( $\chi^2 = 11.831$ ,  $df = 1$ ,  $P = 0.0517$ ,  $OR = 0.008$ ).

Variable	Number Analyzed	Number Positive (%)	P-Value
<b>Use of Oral Contraceptives (years)</b>			
1 - 5	67	5 (7.5)	0.3012
6 - 10	21	1 (4.8)	
> 10	30	3 (10.0)	
Never used	158	15 (9.5)	
<b>Smoking</b>			
Yes	4	1 (25.0)	0.0150
No	272	23 (8.4)	
<b>Infection with HIV</b>			
Yes	16	2 (12.5)	0.0517
No	260	22 (8.5)	
<b>Use of Sex Enhancers</b>			
Yes	11	1 (9.1)	0.0638
No	265	23 (8.7)	

**Table 4:** Distribution of human papilloma viruses based on some risk factors among women in Kaduna state.

There were 11 of the respondents that used sexual enhancers out of which one had HPV infection, however, there was no statistical association between HPV infection and the use of sexual enhancers ( $\chi^2 = 8.397$ ,  $df = 1$ ,  $P = 0.0638$ ,  $OR = 0.002$ ).

Some women presented some clinical manifestations that could possibly suggest cervical neoplasia or cancer. Looking at some of these features (Figure 1), it was observed that women that had inter-menstrual bleeding had a higher HPV prevalence (12.5%: 5/40) compared to those that did not (8.1%: 19/265), with a significant association ( $\chi^2 = 24.112$ ,  $df = 1$ ,  $P = 0.0058$ ,  $OR = 0.07$ ). Also, women that complaint of post coital bleeding had a higher infection rate (33.3%: 2/6) than those that did not (8.1%: 22/270), with a significant association ( $\chi^2 = 25.000$ ,  $df = 1$ ,  $P = 0.0011$ ,  $OR = 0.008$ ). The women that complaint of pain during coitus had a higher infection rate (26.7%: 4/15) than those that did not (7.7%: 20/251), with a significant association ( $\chi^2 = 25.601$ ,  $df = 1$ ,  $P = 0.0048$ ,  $OR = 0.080$ ).



**Figure 1:** Relationship between human papilloma viruses and some clinical features suggestive of cervical cancer, among women in Kaduna state, Nigeria.

Key: IMB: Inter-Menstrual Bleeding; PCB: Post-Coital Bleeding; PDC: Pain During Coitus

## Discussion

The prevalence of HPV obtained in this study was 8.7%. This is much higher than the 4.0% and 1.2% in reported in Ibadan [16] and Enugu [17] but slightly lower than then 10.7% reported in Maiduguri [18] and 10.3% reported in Imo State [19]. The obtained prevalence is much more lower than 26.3%, 32% and 48% reported in Ibadan, Tanzania and Brazil respectively [20-22]. The differences in all these prevalence rates may be because of differences in the socio-cultural factors of the studied populations and the different diagnostic methods employed which include ELISA, Cytology, PCR, 21 HPV Geno array test kit among others, and these diagnostic methods have varying degrees of sensitivities. The prevalence obtained from this study is appreciable, which implies that HPV is actively circulating in the region. The HPV infection in these women may persist and result to the development of precancerous lesions and eventual cancer. Therefore, women that were positive were advised to go for Pap smear test and then see a physician for appropriate action. The high HPV prevalence in the study area also necessitate increasing the level of awareness on HPV infection and its predisposing factors.

Human Papilloma Virus infection was found to be highest in participants that were between ages 27 - 36, which is similar to the findings of Christine and Holscheider [23], Aminu *et al.* [24] and Ojiyi *et al.* [18] but contrast those of Nuacler *et al.* [25] and Ziziphor *et al.* [26]. Age was found to be statistically associated with HPV infection and this does not agree with the findings of Ojiyi *et al.* [18]. The higher HPV prevalence observed in younger women could be as a result of the high rate of sexual activity commonly observed in the younger ones as earlier reported by Tom and Miller [27] and it could also be that they recently acquired the infection, not long enough for it to have regressed.

Human Papilloma virus infection was not seen in the single respondents, this could be because most of them take protective measures when having sex with their partners due to their fear of getting pregnant or contracting sexually-transmitted infections. It could also be due to the small number of single women enrolled in the study. Human Papilloma Virus infection on the other hand was higher in the married women, and this could be because most married women do have sex without protection, thereby exposing themselves to sexually-transmitted viruses like HPV.

The observation that women that never went beyond secondary school had the highest rate of infection could be due to an increased level of awareness on ways of contracting and preventing STI's by these women as they advance in education. This observation is similar to that made by Naucler *et al.* [25].

There was no statistically significant association between HPV infection and occupation of Ojiyi *et al.* [18] that reported a statistically significant association between occupation and cervical HPV infection. Women that were farmers as well as those that were into business had the highest rate of HPV infection while the civil servants had the lowest. This finding could be due to a low socio-economic status as most of the women were peasant farmers and petty traders. It is generally accepted that poor socio-economic status could lead one to indulge in some risky lifestyles such as promiscuity [28]. Promiscuity entails having many brief sexual relationships. When one is promiscuous, they have multiple sexual partners, which increases their chances of contracting HPV infection.

Most of the women in this study were in a monogamous marriage, HPV infection was however, higher in the few that were in a polygamous marriage, and marriage type was highly associated with HPV infection. This observation could be accounted for by the fact that such women easily acquire STI's from their spouses who have other sexual partners. In a polygamous marriage, one man marries two or more wives, therefore, if one of the wives in infected with HPV, the man may contract the virus and infect the other wives.

There was a statistically significant association between number of sexual partners and HPV infection. This owe to the fact that the higher the number of sexual partners one has, the more exposed they are to sexually transmitted organisms, HPV inclusive [29]. This agrees with the findings of Ojiyi *et al.* [18] that observed multiple sexual partners and coital frequency to be significantly associated with HPV infection. Women that had multiple sexual partners were 1.4 times more at risk of acquiring HPV infection than women with single

sexual partners. The odds ratio being greater than 1 further affirms the association that exists between number of sexual partners and HPV infection and can further be supported by the association that was observed between HPV and polygamy.

In this study, it was seen that women that were Grand multiparous had the highest rate of HPV infection compared to others. This is because the higher the number of pregnancy, the more likely there was high frequency of sexual contact, which is directly proportional to acquiring the virus. Parity was associated with HPV infection in the study; the higher the number of deliveries, the higher the rate of HPV infection. This finding agrees with the reports of Lor zato *et al.* [30], Ojiyi *et al.* [18], Trotter *et al.* [31], Firnhaber *et al.* [32] and Okolo *et al.* [22] who found multiparous women at significant risk of acquiring genital HPV infection compared to their non-parous counterparts.

Contraceptives are taken by women to prevent conception, however it also place them at a disadvantage especially when taken for a long duration because it (particularly steroid contraceptives) enhances persistence of HPV in cervical epithelial cells which could lead to transformation of those cells [33]. Human Papilloma Virus infection was most prevalent in women that took oral contraceptives for over 10 years with no significant difference. This findings disagrees with those made by Naucler *et al.* [25], Pietro *et al.* [24] and Ojiyi *et al.* [18] that reported a significant association between duration of contraception use and cervical HPV infection.

Further analysis of co-infection of HPV and HIV revealed that women that were infected with HIV had a higher prevalence of HPV compared to women that were not. Co-infection of HIV and HPV would have played a role in HPV persistence in the cervical epithelial cells and the consequent development of cervical lesions [34]. This therefore calls for the establishment of the routine HPV testing alongside HIV, as HPV is strongly associated with the development of SIL [6]. This finding is similar to that of Palefsky and Holly [35], Malik [36], Mendoza *et al.* [37] and Liu *et al.* [38] but not same with the report of Ojiyi *et al.* [18].

In this study, sexual enhancers commonly known as “kayan mata” are substances of all forms, mostly chemical in nature that some women apply in their vagina in other to increase the sexual ecstasy for their partners during sex. These sexual enhancers could contain toxic substances that may enhance viral replication, their pathogenicity or may serve to alter host immune responses to the virus, thereby leading to their persistence in the cervical epithelial cells. Therefore, as much as these substances increase sexual pleasures, they may also promote transformation of the cervical epithelial cells leading to precancerous lesions. Women that used sexual enhancers were 0.002 times more at risk of acquiring HPV infection than women never used it. This implies that there is a possibility, though extremely small that the use of sexual enhancers predisposed to HPV infection.

Some clinical manifestations that could possibly suggest cervical neoplasia or cancer were studied. Analysis of some of these features showed that women that had inter-menstrual bleeding had higher prevalence compared to those that did not. Also, women that complained of post coital bleeding and pain during coitus had higher infection rates. There was a very strong statistical association between HPV infection and these clinical features which is in line with the findings of Ojiyi *et al.* [18].

### Conclusion

The prevalence of HPV obtained from this study have shown that the virus is endemic in the study area, thus necessitating the establishment of HPV awareness campaign programmes, were women will be enlightened on HPV-associated cervical cancer and the need to go for HPV testing. It also emphasizes the need for the incorporation of HPV testing in routine clinical laboratory tests for all persons. Men that turn out HPV-positive will be urged to bring in their partners for testing.

### Acknowledgements

We thank the doctors and nurses of the Obstetrics and Gynecology Department of General Hospital, Kafanchan, Barau Dikko Teaching Hospital, Kaduna and Ahmadu Bello University Teaching Hospital Zaria for their assistance in the collection of samples. We also appreciate the head of the laboratory Department of General Hospital, Kafanchan and Barau Dikko Teaching Hospital, Kaduna for providing the storage facility for the samples collected. We owe a big gratitude to our respondents for accepting to participate in this study.

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**Volume 8 Issue 9 September 2019**

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