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RELEVANT RISK FACTORS FOR CERVICAL CANCER IN UYO, AKWA IBOM STATE, NIGERIA

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ABSTRACT

Background: Human Papilloma Virus has been established as the preeminent etiologic agent for cervical cancer and its precursor lesions. Because of the varying prevalence of the precursor lesions of cervical cancer in different communities, it is possible that the relevant risk factors also differ between communities. **Objective:** This cross-sectional study was carried out to determine the pertinent risk factors of cervical neoplastic lesions in Uyo, Akwa Ibom State. **Methodology:** Four hundred and sixty six consenting females comprising 231 HIV positive women as cases and 235 HIV negative women as controls were recruited and screened for cervical cancer and its precursor lesions using conventional Pap smear between February 2013 and April 2014. A questionnaire was applied to elicit information on every woman's background and relevant risk factors including socio-economic and marital status, menstrual and obstetric history and use of Oral contraceptive pills. **Result:** The study participants were aged between 18-60 years with a mean age of 35.24±9.26 years and 35.63±8.44 years in the HIV-positive and HIV-negative women respectively. Majority of the study participants (95.1% of the HNW and 89.3% of the HPW) were negative for Squamous Intraepithelial Lesions (SILs). The prevalence of abnormal cervical cytology was more than two times higher in the HIV-positive women than in the HIV-negative women (10.6% vs 4.9%, $p<0.05$). In this study, factors noted to be associated with cervical neoplasia include HIV infection and age at first intercourse. There was no significant relationship between age, educational status, menarche, and parity with the frequency of abnormal cervical cytology in both groups of women. **Conclusion:** From this study in Uyo, it can be concluded that HIV infection and age at first intercourse are important risk factors in the development of cervical dysplasia in this region. On multivariate analysis, the only independent risk factor for cervical neoplasia was age at first intercourse.

KEYWORDS: HIV, neoplasia, precursor.

INTRODUCTION

About 500,000 new cases of cervical cancers are recorded each year.[1] More than 85% of all cervical cancer related deaths occur in developing countries like Nigeria, where it is the second most common cause of cancer related deaths in women and an important cause of cancer mortality in young women.[1]

HPV is the preeminent aetiological agent of cervical cancer while other associated factors are regarded as risk factors.[2] Epidemiological studies have identified possible risk factors for cervical cancer and its precursor lesions. These factors include the following: Sexual activity (Number of sexual partners and early onset of sexual activity especially below 16 years during the period of active development of the cervical transformation zone); Sexually Transmitted Diseases *(Human Papillomavirus, Herpes simplex Virus, Chlamydia trachomatis); Human Immunodeficiency Virus (HIV)*; Early age at first pregnancy; High parity; Low socioeconomic class; Cigarette smoking; Immunosuppression from any cause; Vitamin deficiency (eg folic acid); Oral contraceptives; and Interval since last Pap smear.[3,4] Generally, HPV infection, life time number of sexual partners, and cigarette smoking are considered the major independent risk factors.[3]

Nearly all invasive carcinomas of the cervix are preceded by a stage in which the abnormal cells are confined to the epithelium.[5] This intraepithelial stage can be detected on cytology, and share many of the cytological features of the invasive stage.[5] Squamous Intraepithelial lesion of the uterine cervix is a disease of women in their reproductive years.[3] The prevalence of this disease varies considerably both between and within countries depending on the underlying risk factors in the population and the extent of cytological screening.[3] Generally, there is an age-related decrease in the

prevalence of cervical squamous intraepithelial lesions but invasive cervical cancer is usually seen in women above 40 years.[3]

Because of the lack of national screening programme for cervical cancer and the possible reliance on opportunistic screening, it is important to determine pertinent risk factors for cervical cancer in various regions of Nigeria. This study aims to evaluate relevant risk factors for cervical cancer and its precursor lesions in Uyo, Akwa Ibom state, South-South region of Nigeria.

MATERIALS AND METHODS

This is a cross-sectional, hospital based study that was carried out between February, 2013 and April, 2014 in the University of Uyo Teaching Hospital, Uyo, Akwa Ibom State, South-South geopolitical zone of Nigeria.

A total of 466 ever-married or sexually active women aged between 18-60 years were recruited for this study. They comprise 231 HIV positive and 235 HIV negative women. The women were recruited by word of mouth based on age, family and social history from the HIV, Gynaecology, General Out-Patient, and Family planning clinics of the hospital. Patients bleeding per vaginum and those below 18 years as well as patients on immunosuppressive drugs, those being managed gynaecological malignancies, and pregnant women were excluded.

A questionnaire was applied to obtain information on every woman's background and relevant risk factors including socio-economic and marital status, menstrual and obstetric history and use of oral contraceptive pills.

All the women were screened for cervical cancer by conventional Papanicolaou (Pap) while observing standard precautions and protocols. The 2001 Bethesda System (TBS) of reporting cervical and vaginal cytology was used as the basis for cytology classification.

The study was approved by University of Uyo teaching hospital, Uyo institutional health ethical research committee and all consenting women signed a written informed consent. In line with the ethical statement of this study, individual results were communicated to the participants and appropriate counselling and referral was made were necessary.

RESULTS

Socio-Demographic characteristics of the study population [Tables 1]

The results of 449 women (96.4%) consisting of 226 HPW and 223 HNW were used for statistical analysis.

Tables 1 summarises the socio-demographic characteristics of the study participants. The women were aged between 18-60 years with a mean age of 35.24±9.26 years and 35.63±8.44 years in the HIV negative (HNW) and HIV positive women (HPW) respectively. More than half of the HNW were married (64.1%) and had a secondary or tertiary level of education (75.6%). Only about one-third of the HPW were married (36.7%) but most of them also had a secondary or tertiary level of education (76.1%).

Most of the women in this study attained menarche at or below 14 years (72.6% of the HNW and 67.3% of the HPW) and also had their sexual debut at or below 18 years (55.2% of the HNW and 68.1% of the HPW) but most of the HPW (57.1%) have four and above lifetime number of sexual partners unlike the HNW (39.2%).

The range of parity of the HNW was 0-9 with a mean of 2.28± 2.3 while that of the HPW were 0-11 and 2.0±2.25 respectively. This shows that majority of the participants have a parity between 0 and 2 (57.8% of HNW and 69.5% of HNW). Only about one-tenth of the participants in both groups had ever used combined oral contraceptive pills while about one-third of them occasionally take alcohol. Most of the study participants are non-smokers (99.6% of HNW and 99.1% of HPW).

There was poor awareness about cervical cancer and Pap smear in the study population as is the utilization on Pap smear. About 40% of the HNW are aware of cervical cancer but only 9.0% of them know about Pap smear screening test. Despite the knowledge, only 8 of the women (3.6%) have ever done a Pap smear. The finding is even worse among the HPW as only 11.5 % of them know about cervical cancer, 3.1% of them know about Pap smear and less than 1% of them have ever done a Pap smear.

Pap smear results [Table 2]

The prevalence of cervical epithelial cell abnormality in this study is 4.9% in the HNW and 10.7% in the HPW and shows that there is a significant relationship between HIV status and abnormal Pap test result ($p < 0.05$), [see table 2].

Out of the 231 HPW, 202 (89.3%) were negative for Squamous Intraepithelial Lesions (NILM) while the rest were sub-classified as ASCUS (6 cases, 2.7%), LGSIL (13cases, 5.6 %), HGSIL (5 cases, 2.2%). Five of the HPW (2.2%) had an inadequate smear due to scant cellularity and excessive mucus obscuring the squamous epithelial cells while 22 (10.9%) of the HPW with NILM had inflammatory smear (This represents 9.7% of the total HPW). There was no case of cervical cancer in the HPW. Among the HNW, 212 participants (95.1%) were negative for Squamous Intraepithelial Lesion/ Malignancy (NILM) while the rest were classified as ASCUS (4 cases, 1.8%), LGSIL (3 cases, 1.35%), HGSIL (3 cases, 1.35%), and Squamous cell carcinoma (1 case, 0.4%). Twelve (5.7%) of the HNW with a negative report had inflammatory smear (This represents 5.4% of the total HNW).

Age distribution of Pap smear result and age specific prevalence rate [Tables 3 and 4]

The age distribution of the Pap smear results in this study shows that the age groups with the worst abnormal cervical epithelial cytology according to HIV status were age groups 25-31 and 39 – 45 years in the HPW and 32 – 38 years in the HNW [see table 3]. The age specific prevalence rate was highest among women that are 46 years and above in both the HNW and HPW (14.7% and 16.7% respectively) [see table 4].

Table 1: Socio-demographic characteristics of study participants.

Characteristics	HNW (n=223)	HPW (n=226)
Age	Number (%)	Number (%)
18-24	15 (6.7)	14 (6.2)
25-31	61 (27.4)	61 (27.0)
32-38	64 (28.7)	62 (27.4)
39-45	49(22.0)	53 (23.5)
≥ 46	34 (15.2)	36 (15.9)
Menarche		
≤ 14	162 (72.6)	152 (67.3)
≥ 15	61(27.4)	74 (32.7)
First intercourse		
≤ 18	123(55.2)	154 (68.1)
≥ 19	100 (44.8)	72 (31.9)
Number of sexual partners		
1_3	136 (61.0)	97 (42.9)
≥ 4	87 (39.0)	129 (57.1)
Parity		
0-2	129 (57.8)	157 (69.5)
3_5	73 (32.7)	51 (22.6)
≥ 6	21 (9.4)	18(8.0)
Use of oral contraceptives		
yes	29 (13.0)	24 (10.6)
No	194 (87.0)	202 (89.4)
Alcohol intake		
Yes	96 (43.0)	74 (32.7)
No	127 (57.0)	152 (67.3)
Smoking history		
Yes	1 (0.4)	2 (0.9)
No	222 (99.6)	224 (99.1)

Table 2: Pap smear result in relation to HIV status.

Pap Test Result	HIV STATUS		chi-square	p value
	HNW No. (%)	HPW No. (%)		
NILM	212 (95.1)	202 (89.3)	12.12	0.03
ASC-US	4 (1.8)	6 (2.7)		
LGSIL	3 (1.3)	13 (5.8)		
HGSIL	3 (1.3)	5 (2.2)		
SQCC	1 (0.4)	0 (0)		
TOTAL	**223 (100)**	**226 (100)**		

Key: NILM (negative for squamous intraepithelial lesion/malignancy), ASC-US(atypical squamous cells of uncertain significance), LGSIL (low grade suamous intraepithelial lesion), HGSIL (high grade squamous intraepithelial lesion), SQCC (squamous cell carcinoma). HPW (hiv positive women), HNW (hiv negative women). Five smears of HPW were inadequate.

Table 3: Distribution of Pap test result in relation to age and HIV status.

HIV Status	AGE Group	PAP Smear Result in Number and (%)					
		NILM-I	NILM	ASCUS	LGSIL	HGSIL	SQCC
HNW	**18 - 24**	0 (0)	15 (7.5)	0 (0)	0 (0)	0 (0)	0 (0)
	25 - 31	3 (25.0)	55 (27.5)	0 (0)	2 (66.7)	1 (33.3)	0(0)
	32 - 38	3 (25.0)	59 (29.5)	1 (25.0)	0 (0)	0 (0)	1 (100)

	39 - 45	5 (41.7)	43 (21.5)	0 (0)	0 (0)	1 (33.3)	0 (0)
	≥46	1 (8.3)	28 (14.0)	3 (75.0)	1 (33.3)	1 (33.3)	0 (0)
	Total	**12 (100)**	**200 (100)**	**4 (100)**	**3 (100)**	**3(100)**	**1 (100)**
HPW	**18 - 24**	1 (4.5)	11 (6.1)	2 (33.3)	0 (0)	0 (0)	0 (0)
	25 - 31	4 (18.2)	52 (28.9)	1 (16.7)	2 (15.4)	2 (40.0)	0 (0)
	32 -38	2 (9.1)	51 (28.3)	1 (16.7)	6 (46.2)	1 (20.0)	0 (0)
	39 - 45	8 (36.4)	39 (21.7)	0 (0)	1 (7.7)	2 (40.0)	0 (0)
	≥46	7 (31.8)	27 (15.0)	2 (33.3)	4 (30.8)	0 (0)	0 (0)
	Total	**22 (100.0)**	**186 (100.)**	**6(100)**	**13 (100.0)**	**5 (100.0)**	**0 (0)**

KEY: HNW [HIV negative women], HPW [HIV positive women], NILM [negative for squamous intraepithelial lesion/malignancy], NILM-I [nilm with inflammatory smear], LGSIL [low grade squamous intraepithelial lesion], HGSIL [high grade suamous intraepithelial lesion], SQCC [invasive suamous cell cervical cancer].

Table 4: Age specific prevalence rate of abnormal smear in relation to HIV status.

	Age Group	**No. Screened**	**No. Positive**	**Age Specific Prevalence (%)**
HNW	18-24	15	0	0
	25-31	61	3	4.9
	32-38	64	2	3.1
	39-45	49	1	2
	≥46	34	5	14.7
	Total	**223**	**11**	
HPW	18-24	14	2	14.3
	25-31	61	5	8.2
	32-38	62	8	12.9
	39-45	53	3	5.7
	≥46	36	6	16.7
	Total	**226**	**24**	

DISCUSSION

The study participants were aged between 18 and 60 years with a mean age of 35.24±9.26 and 35.63±8.44 in HNW and HPW respectively. The mean age and age range seen in this study was similar to those noted in related studies.[6,7]

Most of the HNW were married (64.1%) while majority of the HPW were single, divorced or widowed (63.3%). More HNW had a tertiary education than HPW (50.5% vs 39.8%). The higher level of educated HNW is significant as they are more likely to be gainfully employed, enlightened about cervical cancer and afford regular routine screening, use safe sex practices and have fewer incidences of sexually transmitted infections including cervical precancerous lesions as noted in this study. This agrees with the findings from other studies that showed that HIV-infected women are more likely to be unemployed and trade sex for money or drugs and have more numbers of life time sexual partners.[6,8]

Majority of the women had their menarche before the age of 14 years (72.6% of the HNW and 67.3% of the HPW) but more HPW had sexual debut before the age of 18 years (68.1% vs 55.2%) and four or more numbers of life time sexual partners (57.1% vs 39.0%). This is important because early age at sexual debut and multiple sexual partners are risk factors for cervical neoplasia. This finding is similar to that reported in Maiduguri by Chama et al where the population studied were generally promiscuous with more than 90% of them having multiple sexual partners.[9]

The mean parity reported in this study was 2.28±2.3 (range 0-9) and 2.0±2.25 (range 0-11) in the HNW and HPW respectively. The use of alcohol and tobacco as well as the use of oral contraceptive pill is low in both groups of study participants. This study also showed that the knowledge about cervical cancer and Pap smear is generally poor in this region. Only about 40% of the HNW and 11.5% of the HPW were aware of cervical cancer while only 9% of the HNW and 3.1% of the HPW know about the screening method by Pap smear. A study by Mbamara et al in Nnewi, Eastern Nigeria, also reported that only 12.9% of the study population were aware of cervical cancer screening test.[10] This finding is important as knowledge about cervical cancer and its preventive measures is one way of increasing the utilization of the available screening protocols and decreasing the incidence of cervical cancer.

The result of Pap smear cytology in this study showed that the prevalence of abnormal cervical epithelial cytology is two times higher in HPW compared to the HNW (%10.6 Vs 4.9%; P<0.05; OR 2.3, 95% CI 0.9-5.5). The prevalence of cervical dysplasia in women living with HIV/AIDS varies with several studies in different environment ranging from 10.2%[11] to 34%.[12]

Studies in the general population have reported lower prevalence. A study in the Jewish population of women reported a low prevalence of 0.98%[11] while reports from northern regions of Nigeria gave a range of prevalence from 4.8% to 14% in the general population.[13-16]

The higher prevalence of abnormal cervical epithelial cytology in HPW reported in this study agrees with the reports from other studies done in Nigeria.[9,17-19] Some studies have shown a marked difference in the prevalence rate. Geographical differences in the prevalence of HPV infection may explain the differences in the prevalence of cervical dysplasia seen in women living with HIV/AIDS from different studies. Whatever the prevalence obtained, these studies have shown that women living with HIV/AIDS have a higher prevalence of cervical disease and therefore strenghtens the need to include regular cervical cancer screening as part of the protocol for the management of HIV patients in this region.

Genital infection with high risk types of Human papillomavirus is the primary etiologic agent of cervical cancer and its precursor lesions while HIV infection is a risk factor.[20] Several interactions between HPV and HIV exist to explain why HIV-infected women have a higher prevalence of cervical dysplasia and these includes : reduced local cervical cellular mediated immunity from generalized immunosuppression causing persistence of HPV infection, direct viral-viral interaction which may enhance transcription of HPV oncoproteins, and increased immune escape pathways.[20]

The frequency of inflammatory smears and all categories of SILs, especially the high grade SILs were higher in the HPW. This finding is supported by similar findings in the studies by Agaba et al,[17] Dim et al,[21] Bassey et al,[22] and Anorlu et al.[7] Inflammatory conditions of the cervix are risk factors for both HIV infection and HPV associated cervical disease. Some HPW may care less about using safe sex practices because of their HIV status which may explain the higher prevalence of inflammatory smears observed in this and other studies. There is also the problem of lowered local cervical immunity that may also explain the persistence of cervical infections despite antibiotic treatment. HIV-induced inflammatory responses may interfere with a woman's ability to mount an effective immune response to HPV and other microbial infections.[23]

The pathogenesis of cervical cancer is multifactorial with several studies showing that young age at first intercourse, multiple sexual partners, high parity, cigarette smoking, race, and low socio-economic status are important risk factors.[24] This study has shown that HIV infection is a risk factor in cervical neoplasia. On multivariate regression analysis only the age at first intercourse contributed significantly to the positivity of Pap smear in both groups of women. Sexual debut before the age of 18 years is an important risk factor since this is the period of formation of the Transformation zone. Other studies have also shown that early onset of sexual debut is an important risk factor for cervical cancer in African women.[25,26] There was no significant relationship between age, educational status, menarche, and parity with the frequency of abnormal cervical cytology in both groups of study participants. These findings differ from the reported risk factors of cervical neoplasia in literature, but supports the fact that the main etiologic factor of cervical cancer is anogenital infection with high-risk types of HPV and all other factors are risk factors. The progression from HPV infection to cervical neoplasia takes an average of 10-20 years as reported by some researchers.[27] This long interval between HPV infection and the development of cervical neoplasia may explain why the highest age specific prevalence rate of abnormal cervical cytology was found among women that were 46 years and above in this study [see table 4].

This is a hospital-based study and the findings may not be representative of what is obtained in the general population. A population-based study in this environment may depict a more accurate prevalence of cervical neoplasia. The prevalence of cervical HPV infection according to HIV status needs to be determined in this region.

From this study in Uyo, it can be concluded that HIV infection and age at first intercourse are important risk factors in the development of cervical dysplasia.

The current campaign about HIV awareness should be sustained and broadened so as to get more people to initiate treatment before the onset of severe immunosuppression that predispose to opportunistic infections and neoplasia. Finally, there is a need for more epidemiological studies on cervical cancer and its precancerous lesions in this region. This should include genital HPV testing so as to improve the understanding of the incidence and risk factors of cervical cancer in this region.

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