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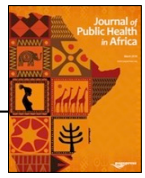

ORIGINAL ARTICLE

Prevalence and predictors of squamous intraepithelial lesions in human immunodeficiency virus positive women in Sagamu, southwest Nigeria

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Abstract

Background: Cervical cancer is still a public health problem in many developing countries, like Nigeria. HIV infection makes HPV infections last longer, progress to squamous intraepithelial lesion of the cervix, and eventually lead to invasive cervical cancer.

Objective. Find out how often squamous intraepithelial lesions (SIL) happen and what causes them in HIV-positive women in Sagamu, southwest Nigeria.

Methods. A cross-sectional study was done with 165 women with HIV and 165 women without HIV. Pap smears were done on all of the people in the study. The data was looked at with IBM-SPSS Windows v. 23.

Results: Both groups were about the same age and had the same number of children (P=0.194 and P=0.388, respectively). The participants' average age (SD) was 36.8 (5.6), and the median number of children they had was 3. HIV-positive women were much more likely to have an abnormal cytology smear (24.8%) than HIV-negative women (7.3%) (2 = 18.904, P 0.001). There wasn't a link between having HIV and the severity of cervical lesions (2 = 3.66, P = 0.162). A CD4 cell count of less than 350 cells/mm^{3}was found to be a strong predictor of an abnormal cervical cytological smear in HIV-positive women (AOR: 25.5; CI: 8.8-73.5; P 0.001).

Conclusion. In Sagamu, Nigeria, the number of HIV-positive women with SIL of the cervix was much higher than the number of HIV-negative women with SIL of the cervix. HIV-positive women, especially those with a low number of CD4 cells, need cervical smear tests more often. This will make sure that pre-invasive lesions are found and treated as soon as possible.

Keywords: Cervical cancer, HIV, HPV, Squamous intraepithelial lesion, Prevalence

INTRODUCTION

Cervical cancer is the fourth leading cause of cancer and death in women worldwide.[1] In Nigeria, 36 per 100,000 women of reproductive age develop cervical cancer. Due to its 10- to 15-year pre-invasive period, cervical cancer is preventable and treatable. Nigeria has 4.8% to 14% precancerous lesions.[2–4] In wealthy countries, population screening makes cervical cancer rare.[5] Low risk perception, lack of understanding about cervical cancer screening, and poor access to screening for early detection contribute to cervical cancer incidence and mortality in underdeveloped nations.[5]

Human papillomavirus (HPV) causes squamous intraepithelial lesions of the cervix and invasive cervical cancer. Sub-Saharan Africa has a higher prevalence of HPV 45 and 35 than other regions. Young age at first sexual encounter, multiple sexual partners, male partner with multiple sexual partners, low socio-economic status, smoking, long-term use of hormonal contraceptives, and immunosuppression, especially HIV infection, accelerate progression from persistent hrHPV infection to squamous intraepithelial lesion of the cervix and invasive cervical cancer.[8]

Sub-Saharan Africa has more than two-thirds of the world's HIV-positive population.[9,10] Nigeria has 9% of the world's HIV population, or 3 million people. HIV and HPV can be contracted simultaneously. HIV increases hrHPV persistence and preinvasive cervical lesions.[11,12] Southwest Nigerian HIV-positive women have few data on SIL predictors. This study examined the prevalence and determinants of squamous intraepithelial lesions in HIV-positive women in Sagamu, Nigeria.

MATERIALS AND METHODS

The study was conducted in Olabisi Onabanjo University Teaching Hospital (OOUTH) Sagamu, Ogun State, Nigeria. The hospital serves as referral centre for Obstetrics and Gynaecological services for neighbouring towns and villages of Ogun and Lagos States in southwest Nigeria. The study was a comparative cross-sectional study involving two groups: HIV positive women attending Virology Clinic and HIV negative women attending Gynecology Outpatient and Family Planning Clinics of OOUTH. Pregnant women, women in puerperium, women with obvious cervical lesions or cancer of the lower genital tract, and women with prior history of treatment for pre-cancerous and cancerous lesions of the cervix were excluded from the study.

The minimal sample size (n) was determined using the formula for comparison between two groups when the end point is qualitative.[13] Sample size $n = 2(Z_{\alpha/2} + Z_{\beta})^2 P(1-P) / (P_1-P_2)^2$ where $Z_{\alpha/2}$ at 0.05 significance =1.96; Z_{β} at power of 80% = 0.84, P_1 and P_2 = proportion of squamous intraepithelial lesion of cervix in the two groups and $P = (P_1 + P_2)/2$. In a previous study,[14] the prevalence of squamous intraepithelial lesion of the cervix in the HIV positive and HIV negative women were 14.3%and 3.3% respectively. The calculated sample size was 104 for each group, however, 165 women were recruited into each group to cater for any attrition.

Eligible HIV positive women were recruited from the virology clinic while HIV negative women matched for age and parity were recruited from the Gynecology Outpatients and Family Planning Clinics of OOUTH. HIV status was determined using Determine HIV screening kit (Alere, Japan) after a pre-test counselling. Post-test counselling was also done after the screening test. The study participants were recruited consecutively until the sample size was reached.

Ethical considerations

Ethical approval for the study was obtained from the Health Research and Ethics Committee of the Olabisi Onabanjo University Teaching Hospital, Sagamu

Supplementary information The online version of this article (Figures/Tables) contains supplementary material, which is available to authorized users.

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(OOUTH/HREC/185/2017). The research was conducted in accordance with the World Medical the study, and those who agreed to participate were requested to sign a written informed consent form. Data were anonymised by removing all participant identifiers and assigning numbers to each participants.

Data Collection

Data was collected at the various clinics with the aid of a research proforma. Information obtained included demographic characteristics, obstetrics history, gynaecological history, contraceptive history, sexual history and history of smoking. All consenting women had their blood samples collected for CD4 cell count which was measured using flow-cytometry (Partac, Germany). Samples for Papanicolaou smear were also taken on the same day.

Specimen collection and processing techniques

Papanicolaou smear was taken from all study participants. Each participant was placed in dorsal lithotomy position. A clean bivalve vaginal speculum lubricated with water was introduced into the vagina to expose the cervix. The cervix was assessed and examined for gross lesions and abnormal discharge. Cervical smear was taken using Ayre's spatula rotated 360° in a clockwise direction. Smears were made on two points on pre-labelled glass slides and then fixed immediately in 95% alcohol in coupling jars. The smears were sent to the cytology unit of Morbid Anatomy and Histopathology Department of OOUTH for staining and microscopic examination.

All the slides were stained using the Papanicolaou staining technique. The fixed slides were first stained in Harris haematoxylin. The smears were then decolorized with hydrochloric acid water and rinsed in running water. The smears were then stained with orange G6 solution and finally with Eosin Azure 5.0. The slides were further rinsed twice in 95% alcohol, cleared in xylene and mounted in a neutral synthetic resin medium.

The slides were reported in accordance with the 2014 Bethesda classification.[15] The study participants were classified into two groups based on the cytology results: women whose smears were negative for intraepithelial lesion or malignancy and women with epithelial cell abnormalities.

Data analysis

Data were analysed using statistical package for social science (IBM-SPSS) v. 23. Continuous variables were summarised using descriptive statistics such as mean, standard deviation, median and interquartile range (IQR) as appropriate while categorical variables were summarized using frequencies and proportions. The mean and median of continuous variables in HIV positive and HIV negative were compared using independent sample T-test and median test as appropriate. The association between predictor categorical variables and abnormal cervical cytology smears in HIV positive women was determined using Chi square test and Fisher's exact test where necessary. Logistic regression analysis was used to identify the predictors of abnormal cervical cytology smear in HIV positive women after controlling for cofounders. Level of significance was set at $p<0.05$.

RESULTS

The socio-demographic characteristics of all the study participants are depicted in Table 1. The mean age (±S.D.) was 36.8 (±5.6) while the median parity was 3 (IQR 1-4). The distribution of age and parity of the study participants were comparable in both HIV positive and negative women (P=0.194, P=0.388 respectively). Similarly, there was no statistically significant difference between the mean age and median parity of both groups (P=0.309, P=0.275 respectively). Majority of the study participants were between the age range 30-39 years and parity range of 1-2. More than half of the study participants had at least secondary level education. The mean age at coitarche (±SD) was 21.2±4.0, with a range of 15-34 years. The mean age at coitarche was significantly lower in HIV positive women compared with HIV negative women (20.4±3.8 versus 21.9±4.2; P< 0.001). However, the proportion of women who had multiple sexual partners were significantly higher

in HIV positive women compared to HIV negative women (x^2 =28.183; P <0.001). Majority of the study participants were married and non-smokers. Out of the 165 HIV positive women, 156 (94.5%) were on antiretroviral therapy (ART) while 9 (5.5%) were yet to commence the drugs.

The cytology smear result of HIV positive and negative women is depicted in Table 2. Forty one HIV positive women (24.8%) had smear results which were positive for squamous intraepithelial lesion compared to 12 (7.3%) of HIV negative women. Further analysis shows that the proportion of women with abnormal cytology smear was significantly higher in HIV positive women (24.8%) compared to HIV negative women (7.3%) (x^2 = 18.904, P value < 0.001). Eight HIV positive women (4.8%) had smear result showing HGSIL compared to 2 (1.2%) of HIV negative women. The was no statistically significant association between HIV status and severity of cervical lesion (x^2 = 3.667, P =0.162) hows the association between predictor variables and cervical cytology smear result in HIV positive women. Women with CD4 cell count less than 350 cells/mm^3 had a statistically significant increased risk of having abnormal cervical cytological smear when compared with women with CD4 cell count greater than or equal to 350 cells/mm^3 (x^2 = 57.250; P<0.001)(Table 3). The other variable such as age, parity, educational status, age at coitarche, number of sexual partners and use of ART had no significant association with the occurrence of abnormal cervical cytological smear (P< 0.05). On logistic regression analysis (Table 4), after controlling for potential confounders such as age, educational status, age at coitarche, number of sexual partners and use of ART, CD4 cell count less than 350 cells/mm^3 was found to be a significant predictor of abnormal cervical cytological smear in HIV positive women (AOR 25.5; CI 8.8-73.5; P <0.001).

DISCUSSION

In many countries in sub-Saharan Africa, cervical cancer remains a public health concern, unlike in many developed nations where a well-established and effective screening program has reversed the trend.[11,16] Immunosuppression due to conditions such as HIV infection is recognized as a cancer risk factor.[17] This study compared the prevalence of abnormal cervical cytological smears between HIV-positive and HIV-negative women and found that HIV-positive women had a significantly higher prevalence of squamous intraepithelial lesions.

Age, parity, marital status, and smoking behavior were comparable between the two groups studied. However, we discovered that HIV-positive women had significantly lower educational attainment. A similar study conducted in Abuja, Nigeria found comparable results.[18] There is evidence that educational attainment is a significant determinant of HIV infection, with the likelihood of infection increasing for those with a low level of education.[19] In addition, there is a well-known correlation between low educational attainment and low socioeconomic status, and poverty has been identified as a factor that facilitates HIV infection in Nigeria.[12] This may partially explain why HIV-positive women have low educational attainment levels.

In this study, the prevalence of SIL in HIV-positive women was 24.8% and in HIV-negative women it was 7.3%. This is consistent with similar research conducted in other Nigerian cities. Specifically, a study conducted in Abuja reported a prevalence of 26.6% among HIV-positive women, while a study conducted in Kano reported a prevalence of 8% among HIV-negative women.[16,18]

This study found that HIV-positive women were three times more likely to develop pre-invasive cervical lesions than HIV-negative women. Other researchers in Nigeria have reached comparable conclusions.[12,16–18] HIV-infected individuals have a higher risk of acquiring and maintaining high-risk oncogenic HPV strains than HIV-negative individuals. HIV-infected women have a higher risk of developing precancerous cervical lesions as a result of genital HPV infection,[20,21] respectively.[11,22] In low- and middle-income countries, the disparities in pre-invasive and invasive cervical cancer incidence between HIV-positive and HIV-negative women are greatest (LMICS).[23] In Africa, where cervical cancer is the leading cause of cancer death, HIV-positive women are six times more likely to develop cervical cancer than uninfected women.[24] Clinicians

caring for HIV-positive women should therefore pay greater attention to cervical health in this population.

This study revealed that LGSIL was the most prevalent cervical lesion in HIV-positive women, accounting for over fifty percent of abnormal smears in the group. Other researchers have reported similar results.[11,25] This implies that frequent cervical screening in this population of women will facilitate the early detection and treatment of precancerous lesions.

This study examined the relationship between HIV-positive women's cervical cytology smear results and certain predictor variables. It was discovered that the CD4 cell count of HIV-positive women is a strong predictor of an abnormal cervical cytology smear. In particular, the odds of having an abnormal cervical cytology were 25 times greater in women with a CD4 cell count of less than 350 cells per milliliter. This is consistent with additional studies.[25,26] HIV infection is associated with cell-mediated immune dysfunction, which diminishes the body's capacity to clear HPV from cervical tissues.[11] The persistence of oncogenic HPV strains in cervical tissue will inevitably result in the formation of premalignant cervical lesions.[12] In this investigation, there was no correlation between HAART use and abnormal cervical cytology. This is likely due to the fact that nearly all HIV-positive study participants had begun antiretroviral therapy for varying lengths of time prior to enrollment. While some studies have not demonstrated a significant effect of HAART on the prevalence of squamous intraepithelial lesion, others have shown that women on HAART are less likely to develop persistent HPV infection and high grade squamous intraepithelial lesions of the cervix than women who are not on treatment.[26,27] It appears that the beneficial effect of HAART is observed when the drugs are initiated early (prior to advanced disease) and adhered to properly.[27,28]

HIV-positive women's age, number of sexual partners, parity, age at coitarche, and educational status were not significantly associated with abnormal cervical cytology smear results. Recognized risk factors for premalignant and malignant cervical lesions include advanced age, high parity, and multiple sexual partners, presumably due to an increased risk of HPV acquisition in these circumstances.[29] Some researchers have suggested that impaired clearance and reactivation of HPV infection play a larger role than increased HPV acquisition in HIV-positive women.[28,30]This may explain in part the lack of association between these respondents' factors and the incidence of abnormal cervical cytology observed in this study. However, other researchers hypothesize that the extremely high population of oncogenic HPV strains found in HIV-positive women may also reduce the impact of sexual behavior-related factors.[28]

Limitations

The use of HAART in nearly all of the patients may have mitigated some of the effects of HIV on cervical cytology smear results observed in this study. A longitudinal study could have permitted repeated cytology smears and helped to clarify the progression and regression rates of cervical lesions in HIV-positive HPV-infected patients.

CONCLUSION

This study found that in Sagamu, Nigeria, the prevalence of SIL of the cervix was significantly higher among HIV-positive women than among HIV-negative women. In addition, the study revealed that a CD4 cell count of less than 350 cells/mm^3 was a significant predictor of SIL in HIV-positive women. In light of these results, HIV-positive women with a low CD4 cell count must undergo cervical smear testing more frequently. This will ensure early detection and treatment of pre-invasive lesions, thereby aiding in the reduction of cervical cancer among HIV-positive women.

INFORMATION

Authors' contributions. KW conceived and designed the research. AA, OO, PA, and TS conducted the literature review and defined the study's intellectual content. KW was responsible for data collection, while HE was in charge of specimen processing. AA

performed a data analysis. KW composed the initial draft, while AA composed the final version. The final manuscript was read and approved by all authors.

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TABLE 1: Socio-demographic characteristics of study participants

Characteristics	All study participants N(%)	HIV Positive N=165 n(%)	HIV Negative N=165 n(%)	Statistics Test	P-value
Age					
20-29	31 (9.4)	14 (8.5)	17 (10.3)	x^2 =3.283	0.194
30-39	200 (60.6)	94 (57.0)	106 (64.2)		
≥ 40	99 (30)	57 (34.5)	42 (25.5)		
Mean age	36.8±5.6	37.1±5.6	36.5±5.6	T-test =1.019	0.309
Parity					
0	13 (3.9)	7 (4.2)	6 (3.6)	x^2 =3.026	0.388
1-2	150 (45.5)	70 (42.4)	80 (48.5)		
3-4	138 (41.8)	76 (46.1)	62 (37.6)		
≥ 4	29 (8.8)	12 (7.3)	17 (10.3)		
Median parity	3	3	2		0.275
Educational status					
< Secondary level	135 (40.9)	82 (49.7)	53 (32.1)	x^2 =10.542	0.002*
≥Secondary level	195 (59.1)	83 (50.3)	112 (67.9)		
Marital status					
Single	46 (13.9)	20 (12.1)	26 (15.8)	x^2 =2.601	0.272
Married	257 (77.9)	128 (77.6)	129 (78.2)		
Widowed	27 (8.2)	17 (10.3)	10 (6.1)		
Number of sexual partners					
Single	48 (14.5)	7 (4.2)	41 (24.8)	x^2 =28.183	<0.001*
Multiple	282 (85.5)	158 (95.8)	124 (75.2)		
Smoking					
No	320 (97.0)	163 (98.8)	157 (95.2)	x^2 =3.712	0.104
Yes	10 (3.0)	2 (1.2)	8 (4.8)		
Mean age at coitarche	21.1±4.0	20.4±3.8	21.9±4.2	T-test = 3.555	<0.001

**P<0.05 statistically significant.*

TABLE 2: Cervical cytology results of HIV positive and negative women

	HIV Positive	HIV Negative	Chi-square test	P value
Cytology result				
Positive for SIL	41 (24.8)	12 (7.3)	18.904	<0.001
Negative for SIL	124 (75.2)	153 (92.7)		
Category of cervical lesion				
Atypical Squamous cells	12 (7.3)	7 (4.2)	**x^2 = 3.667	0.162
LGSIL	21 (12.7)	3 (1.8)		
HGSIL	8 (4.8)	2 (1.2)		

**P<0.05 statistically significant; **Fisher's exact test.*

TABLE 3: Association between predictor variables and cervical cytology smears result in HIV positive women.

Variable	Abnormal cytology smear	Normal cytology smear	Chi square	P value
Age (years)				
20-29	1	13	4.864	0.088
30-39	21	73		
≥ 40	19	38		
Parity				
≤2	20	57	0.098	0.857
>2	21	67		
Educational Status				
< secondary level	22	60	0.342	0.593
≥Secondary level	19	64		
Age at coitarche (years)				
<20	13	51	1.152	0.356
≥20	28	73		
Sexual Partners				
Single	3	4	**1.270	0.367
Multiple	38	120		
CD4 cell count (cells/mm^3)				
<350	25	8	**57.250	*<0.001
≥ 350	16	116		
Use of ART				
Yes	38	118	**0.367	0.691
No	3	6		

**P<0.05 statistically significant; **Fisher's exact test.*

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TABLE 4: Logistic regression analysis of potential predictors of abnormal cervical cytology smear in HIV positive women.

Variable	AOR	Confidence Interval	P value
Age (years)			
20-29	0.4	0.04-3.9	0.435
30-39	0.7	0.3-2.0	0.591
$\geq$ 40			
Educational Status			
<Secondary level	0.8	0.3-2.0	0.578
$\geq$Secondary level			
Age at coitarche (years)			
<20	1.4	0.5-3.7	0.523
$\geq$20			
CD4 cell count (cell/mm^3)			
<350	25.5	8.9-73.0	<0.001*
$\geq$ 350			
Sexual partners			
Multiple	0.3	0.1-1.8	0.197
Single			
Use of ART			
Yes	0.5	0.1-3.3	0.493
No			

**P<0.05 statistically significant.*

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