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Original Research Article

Prevalence of HIV Infections among Women with Cervical Premalignant Lesions in a Tertiary Health Care Centre

Senthil Kumar S

Associate Professor, Department of Pathology, Madha Medical College and Research Institute, Thandalam, Kovur, Chennai

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Corresponding Author: Dr. Senthil Kumar S
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Abstract:

Introduction: Premalignant cervical lesions have a high risk of developing into cervical cancer. Cervical cancers among women are very common but greatly preventable using simple cervical screening. Women with HIV infection present with increased incidence of cervical cancers but the results are variable. Thus the present study was done to assess the prevalence of premalignant lesion and their association with HIV infections.

Materials and Methods: This cross sectional study was done for duration of 1yr from May 2023 to April 2024 in a tertiary care centre. The case group comprised on 192 randomly selected HIV+ve women and control group comprised on 192 HIV-ve women visiting the tertiary care centre. The socio demographic details of the participants were collected and venous blood was used to check the CD4+ count. The cervical smears were collected using cytobrush and stained with Pap stain and reported according to Bethesda system by a general pathologist as LSIL, HSIL and ASCUS. A p value of <0.001 was considered as statistically significant.

Results: 66% of women were > 50yrs in both Case and control group, 58% in case group and 75% in control group were married (p=0.002). 77% in case group and 69% in control group has completed their schooling and 48% in case group and 34% belonged to low income group (p<0.05). 64% of case group and 57% of control were from rural area and 8% of case and 4% of control were smokers (p>0.05). 44% of case and 32% of controls had their 1st sexual encounter <18yrs; 42% of cases and 28% of controls had multiple sexual partner and 55% of cases and 37% of control used oral contraceptive (p=0.001). 28% of case group showed premalignant cervical lesion of which 72% were LSIL followed by HSIL and ASCUS and 11% of control group showed premalignant cervical lesion of which 71% were LSIL, 19% HSIL and 10% ASCUS (p=0.001). 57% of HIV+ve women had CD4+ count <200/µL and 43% had CD4+ count >200/µL and 79% of HIV+ve women were on HAART therapy.

Conclusion: There was a high prevalence of premalignant cervical lesion in HIV+ve women and LSIL was the most prominently noted grade. There were no cases of squamous cell carcinoma noted. Thus there should be compulsory cervical screening of HIV+ve women along with imparting knowledge and awareness.

Keywords: Cervical carcinoma, Human Immunodeficiency Virus, Papanicolaou stain, premalignant cervical lesion.

Introduction

In 2020 World Health Organization (WHO) reported that 1 in every 10 Indians will acquire cancer in their life time and 1 in 15 will die from it with the overall cancer burden expected to rise by 31.4%.[1] Cervical cancer was the 4th common cancer occurring in women worldwide and the 4th most common cause of death however in India cervical cancer is the second most common cancer and common cause of deaths. India has now surpassed China with highest number of new cases of cervical cancer as well as highest number of deaths from it. [2] Premalignant cervical lesions are associated with a high risk of developing into cervical cancers if left untreated or undiagnosed.[3] Thus early diagnosis of premalignant cervical lesion offers a great opportunity to stop or prevent progression to cervical cancer. A simple non-invasive technique of obtaining smears from cervix aids in early detection of premalignant cervical lesions. Human Papilloma Virus (HPV) infects skin and mucosal surfaces in only humans and causes proliferative lesions. HPV is known to be associated with malignancies of cervix, oral, anal, vaginal, vulvar and skin. Higher incidence of HPV16 and HPV18 infections is noted in premalignant lesions of cervix transforming into cervical carcinomas.[4] The rate of cervical carcinoma increased drastically after the discovery of Human Immunodeficiency Virus (HIV) in infected

women. In 2013 WHO recommended that all women with HIV should have annual screening.[5] HIV infection decreases the ability of the immune cells to detect dysplastic cells hence there is an increased risk of cervical dysplasia leading to premalignant cervical lesion. Thus the aim of the current study was to assess the prevalence of premalignant cervical lesion and their association with HIV infected women visiting a tertiary care center for cervical cancer screening.

Materials and methods

This was a prospective, cross sectional study conducted in a tertiary care center for duration of over a year from May 2023 to April 2024. This study was conducted on 192 randomly selected women visiting the antiretroviral therapy center (ART) in Tertiary Care Hospital were considered as Case group and women who were HIV-ve visiting the tertiary care centre were considered as Control group. All HIV infected women above the age of 18 years were included in the current study whereas women with previous history of hysterectomy or cervical cancer, pregnant and lactating women and women not willing to give cervical sample were excluded from the current study.

Data collection

Written informed consent forms were obtained from all the participants selected for the study. Socio demographic details like age, education status, obstetric and sexual history, nature of ART were collected from selected participants. 192 women who were HIV negative visiting the hospital for a cervical screening was regarded as control group. Venous blood samples were collected in strict aseptic procedure to assess the CD4+ count using flow cytometery. Smears were obtained from the cervix using a cytobrush and were stained with papanicolaou Pap stain. The stained slides were then reported by a Pathologist according to the Bethesda system as low grade squamous intraepithelial lesions (LSIL), high grade squamous intraepithelial lesions (HSIL) and atypical cells of undetermined significance (ASCUS). The dependable variable of the study was presence of premalignant cervical lesion on Pap smear assessed based on Bethesda 2014 classification system. The independent variables were Sociodemographic data collected from participants like age, residence, marital status, education background, economic status, smoking, age of 1st sexual encounter, multiple sexual partners, use of oral contraceptives etc.

All the data obtained were numerically entered into excel sheets and submitted for statistical analysis using SPSS package 22. The association between various participant characteristics and cervical cytological abnormalities between HIV+ve and HIV-ve was assessed using X^2 test. P value of <0.05 was considered as statistically significant.

Heterogeneity in the study was assessed using I^2 statistics and the statistic results of 25%, 50% and 75% were regarded as low, moderate and severe. I2 =75%; (p<0.001)

Results

The current prospective study was conducted among 100% female population. There were 192 HIV positive females as cases and 192 HIV negative cases as controls that were selected based on inclusion and exclusion criteria. Sociodemographic details of participants were noted and samples like venous blood and vaginal smears were collected from all participants. Venous blood samples were used to assess CD4+ count and cervical smears were subjected to Pap test and reported according to Bethesda system as LSIL, HSIL and ASCUS.

Sociodemographic parameters

Out of 192 HIV+ women 12(6%) were below the age of 30yrs, 53(28%) were in range of 30-50yrs and 127 (66%) were above 50yrs of age. Among 192 controls 23(12%) were <30yrs, 71(37%) were 30-50yrs and 98(51%) were > 50yrs of age (p=0.002). (Figure 1)

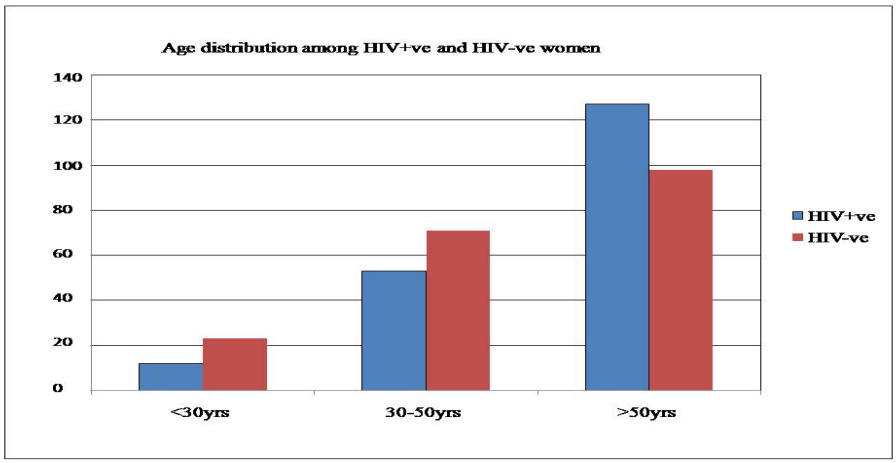

Figure 1: Bar graph showing age distribution among women in Case group and Control Group

111(58%) of HIV+ women were married and 81(21%) were unmarried and in controls 144(75%) were married and remaining 48(25%) were unmarried (p=<0.001). 148(77%) HIV+ women had completed their schooling, 36(19%) were uneducated and 08(4%) had college education whereas in controls 132(69%) had completed their schooling 33(17%) had college education and 27(14%) were uneducated. 92(48%) of HIV+ women belong to low income group, 63(33%) middle income group and 37(19%) belonged to high income group whereas 71(37%) controls belonged to MIG followed by LIG 65(34%) and HIG 56(29%) (p=0.002).

123(64%) of HIV+ women resided in rural areas and 69(36%) in urban areas whereas 192(57%) controls resided in rural and 83(43%) in urban areas (p=0.166). 177(92%) HIV+ women had no history of smoking and 15(8%) had history of smoking whereas in controls 184(96%) had no history of smoking and 08(4%) had history of smoking (p=0.133).

HIV+ women had 1st sexual encounter >18yrs were 108(56%) whereas in controls 131(68%) had 1st sexual encounter >18yrs (p=0.001). 81(42%) of HIV+ women had multiple sexual partner whereas in controls only 28(15%) had multiple sexual partner (p=0.001). 106(55%) HIV+ women used oral contraceptives and 86(45%) did not use oral contraceptives whereas amid controls 121(63%) did not use oral contraceptives and 71(37%) used oral contraceptives (p=0.001). (Table 1)

Table 1:

	Case HIV positive (n=192)	Control HIV negative (n=192)	P value
Age			**0.002****
<30yrs	12 (06%)	23 (12%)	
30-50yrs	53 (28%)	71 (37%)	
>50yrs	127 (66%)	98 (51%)	
Marital Status			**<0.001****
Married	111 (58%)	144 (75%)	
Unmarried	81 (42%)	48 (25%)	
Educational background			**0.001****
Uneducated	36 (19%)	27 (14%)	
Education till Schooling	148 (77%)	132 (69%)	
College education	8 (04%)	33 (17%)	
Socio economic status			**0.002****
Low income group (LIG)	92 (48%)	65 (34%)	
Middle income group (MIG)	63 (33%)	71 (37%)	
High income group (HIG)	37 (19%)	56 (29%)	
Residence			0.166
Rural	123 (64%)	192 (57%)	
Urban	69 (36%)	83 (43%)	
History of smoking			0.133
Yes	15 (08%)	08 (04%)	
No	177 (92%)	184 (96%)	
Age of 1st sexual encounter			**<0.001****
<18yrs	84 (44%)	61 (32%)	
>18yrs	108 (56%)	131 (68%)	
Multiple sexual partners			**<0.001****
Yes	81 (42%)	28 (15%)	
No	111 (58%)	163 (85%)	
Use of Oral contraceptives			**<0.001****
Yes	106 (55%)	71 (37%)	
No	86 (45%)	121 (63%)	
**** Highly statistically significant**			

Table 1 showing Sociodemographic details and reproductive health characteristics of HIV+ and HIV- participants in the present study. The cervical smears of HIV+ smears stained with Pap showed no cervical premalignant lesion in 138(72%) and 54(28%) had cervical premalignant lesion whereas in controls 171(89%) had no cervical lesion and 21(11%) had cervical lesions. LSIL was noted in 39(72%) of HIV + and 15(71%) of controls; HSIL was seen in 10(19%) of HIV+ and 04(19%) and ASCUS was noted in 05(09%) of HIV+ and 02(10%) of controls (p=0.001). (Table 2) (Chart 2) There was no case of cervical carcinoma noted in both groups.

Table 2:

	Case HIV positive (n=192)	Control HIV negative (n=192)	P value
No cervical premalignant lesion	138 (72%)	171 (89%)	----
Had cervical premalignant lesion	54 (28%)	21 (11%)	
LSIL	39 (72%)	15 (71%)	**0.001****
HSIL	10 (19%)	04 (19%)	**0.001****
ASCUS	05 (09%)	02 (10%)	**0.001****
LSIL- low grade squamous intraepithelial lesions; HSIL- high grade squamous intraepithelial lesions; ASCUS- atypical squamous cells of undetermined significance **** Highly statistically significant**			

Table 2 showing premalignant cervical lesions in HIV+ve and HIV-ve participants of the study

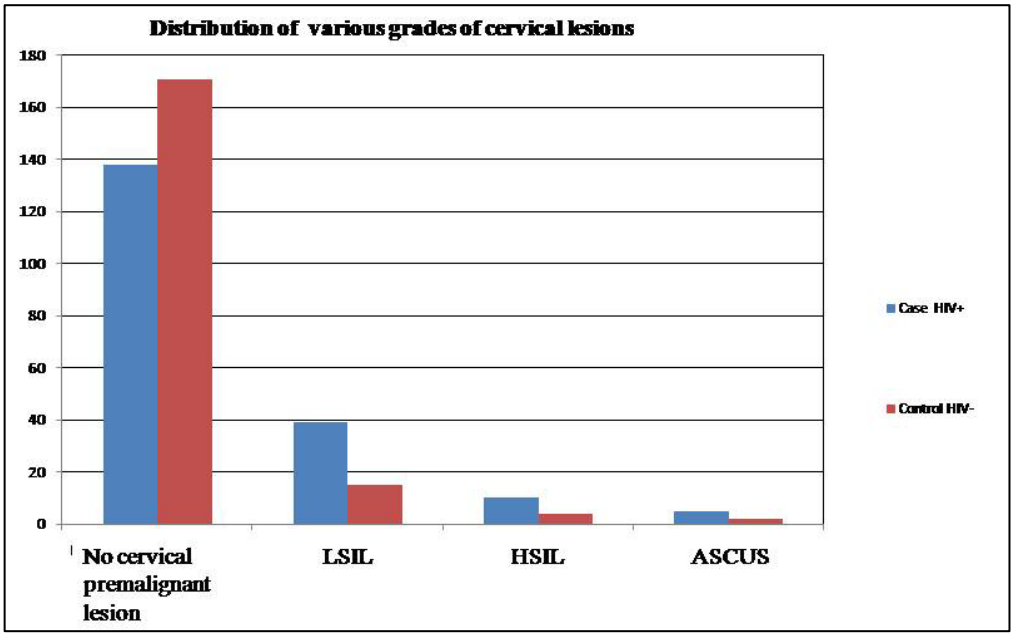

Figure 2: Bar graph showing distribution of various grades of cervical lesions in the study group

In HIV+ women 109(57%) had CD4+ count <200/µL and 83(43%) had CD4+ >200/µL and 152(79%) were currently receiving HAART in HIV+ women and 40(21%) were not receiving HAART. (Table 3)

Table 3:

	Case HIV Positive (n=192)
CD 4+ counts	
<200/µL	109 (57%)
>200/µL	83 (43%)
Currently on HAART	
Yes	152 (79%)
No	40 (21%)

Table 3 showing Immunological characteristics of HIV+ve and HIV-ve participants of the study

Discussion

Cervical carcinoma is the abnormal growth of cells in the cervix with the ability to invade another part of the body and is thought to be caused by high risk HPV.[6] Cervical carcinomas are life threatening and can be easily prevented by early detection using cervical screening. George Papanicolaou was the pioneer in studying the cytological characteristics of the reproductive tract and is known as the father of cervical cancer screening. The commonly used Pap smear also known as Papanicolaou test was invented by him and named after him.[7] High income countries like USA conducted annual screening and were able to identify 94% premalignant cervical lesions and thereby preventing cervical carcinoma.[8] Population based survey from other developed countries showed the effectiveness of screening in preventing cervical cancer. In contrast, systematic review by Mapanga 2017 reported

that there is very little utilization of cervical screening services in developing countries.[9]

Premalignant cervical lesion is the presence of proliferative dysplastic cells confined to the epithelium of the cervix. Premalignant cervical lesions are easier to manage before their progression to cervical cancer. The progression of premalignant cervical lesion to cervical cancer occurs in stages over a period of 10-20yrs from LSIL, HSIL and eventually frank carcinoma. HIV positive women are at a higher risk of developing cervical premalignant lesion as the decrease T-cell activity increases HPV replication and mutation in infected cells and subsequent proliferation of dysplastic cells. Premalignant cervical lesion associated with HIV progress through microsatellite instability whereas in HIV negative the progression is through loss of heterozygosity.[3] Numerous factors play a role in moderating HIV related premalignant cervical lesions like age, 1st sexual encounter, presence of multiple sexual partners, educational and financial background, smoking, use of oral contraceptive etc.

Thus the aim of the current study was to determine the prevalence of premalignant cervical lesions among HIV infected women and compare with women not infected with HIV and also to explore the role of other compounding factors.

The findings of our study show that HIV+ve women showed more prevalence of premalignant cervical lesion in comparison to HIV-ve women and were statistically significant. This finding of our study is consistent with Getinet 2015, Jolly 2017, Mulumba 2018 and Kirabara 2024. Additionally in the current study we also noted that prevalence of cytological abnormalities were significantly higher in women who were HIV+ve than in women who were HIV-ve and is consistent with Ruchika Gupta 2022, Isaakidis 2013, Chakravarty 2016, Mane 2012. The cytological abnormalities of cervical smears considered in present study were LSIL, HSIL, and ASCUS of which LSIL was most prevalent in HIV +ve women and was consistent with other studies. [10]

Majority of the women participating in the study were above 50yrs of age in both HIV+ve and HIV-ve women with least participation of women below 30yrs of age. This finding of ours is consistent with Lemu 2021 who showed that older women are more likely to develop premalignant cervical lesion than younger age females.[11] Contrastingly Kiros 2021 found that women >45yrs of age had a lower chance of developing premalignant cervical lesion.[12] In the current study it was found that majority of HIV+ve women were either uneducated or had education till schooling and were mostly from rural area belonging to low income families and was statistically significant. This is similar to the findings of Ruchika 2022, Chakravarty 2016, Mane 2012. Education, Urban living and financial status are associated with increased knowledge and awareness of diseases prevention and hence reduces chances of acquiring the disease as reflected by studies conducted in Uganda, Rwanda, Ethiopia etc.[10]

Regarding the findings on the use of oral contraceptives, in a study conducted by Oh HY et.al, it was observed that those patients who had a history of severe smoking and concomitant use of oral contraceptives as a consequence had a higher risk of grade II and III intraepithelial neoplasia.[13] Oral contraceptives increase risk of cervical cancer as estrogen and progestin have effect on key HPV proteins.[14]

Tobacco smoking may interfere with regression of cervical precursor lesions. Several experimental studies have demonstrated direct oncogenic effects of chemical tobacco-related carcinogens, while others have reported the modulation of host immunity by tobacco smoking. Tobacco smoking may contribute to cervical carcinogenesis by interfering with regression of HPV-induced lesions rather than by promoting progression as a chemical carcinogen. Cessation of smoking reduces the risk of cervical cancer.[15] Smoking, high parity, long-term hormonal contraceptive use, and co-infection with HIV have been identified as cofactors of precancerous cervical lesions.[16]

In the present study it was noted that HIV+ve women had multiple sexual partner and early age of sexual encounter than HIV-ve women and is consistent to the findings of Lemu 2021. Gessesse 2015, Kiros 2021 suggested that women with single sexual partner or less likely to develop premalignant cervical lesion and that increase in number of sexual partners increases the risk for developing HPV and HIV infection thereby increasing the chances of development of premalignant cervical lesion.[11] HIV-positive women have higher rates of progression to carcinoma and lower rates of regression than HIV-negative women. Compared with HIV-negative women, HIV-positive women have an increased risk of HPV infection and precancerous lesions.

In the current study it was no-ted that HIV viral load is generally high in patients with lower CD4 counts and CD4+ counts were noted to be higher in women who were on HAART. HIV patients on HAART show reduction in HIV viral load hence the CD4+ count is noted to be higher. Studies by Lemu suggest that women who are not receiving HAART have 2.3 times risk of developing premalignant cervical lesion. However Kelly 2018 suggests that HAART controls the viral load and increases life expectancy but unfortunately many women continue to remain susceptible cervical premalignant lesions unlike Kaposi's sarcoma and

non-Hodgkin's lymphoma whose risk reduces with HAART.[17] Contrastingly Liu 2018 reported that HIV+ve women on HAART show lower progression to premalignant cervical lesion.[18] CD4 count of >200 was an important parameter in the study which suggests prevention of precancerous cervical lesion. Clifford GM 2016 suggested that low CD4 counts may be related to the development of cervical carcinomas in HIV+ve women.[19] Based on the findings of the study we would like to propose that HIV acts as an independent factor for higher prevalence of premalignant cervical lesions.

Limitations of the study

The current study was a prospective study and a randomized clinical trial would yield better statistical result. The sample size in the current study is small without follow up. The study did not assess role and subtype of HPV which would shed more light. The current data of the study represents only a small population hence cannot be generalized. Adopting VIA and colposcopy may aid in better identification of cervical lesions than naked eye observation.

Conclusion

In the current study it was note that there was high prevalence of premalignant cervical lesion in HIV+ve women and the LSIL was the most commonly noted premalignant lesion. Though we saw HSIL and ASCUS there was no case of Squamous cell carcinoma noted. Hence recommendation of compulsory cervical screening should be advised to all HIV+ women. We also suggest imparting knowledge and awareness about premalignant cervical lesion may create positive reinforcement for underprivileged women.

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