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SERO-PREVALENCE OF HIV AMONG PATIENTS WITH CERVICAL CANCER MANAGED AT THE TIKUR ANBASSA HOSPITAL ADDIS ABABA, ETHIOPIA
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ABSTRACT

Background: **Cervical cancer is the second most common cancer among women in the world. Globally, according to the 2010 report, 493,243 women diagnosed with cervical cancer and 273, 505 of them died from the disease. It is also the commonest gynecologic cancer in the Ethiopian women. Ethiopia is one of the Sub- Saharan African countries with high HIV prevalence. Studies done in different parts of the world demonstrated clear association between HIV and premalignant cervical lesions but studies on HIV prevalence in invasive cervical cancer are few and showed a wide range of variations.**

Objective: **To determine the sero-prevalence of HIV among patients with histologically confirmed cervical cancer in Addis Ababa, Ethiopia.**

Design: **A facility based cross-sectional descriptive study.**

Setting: **Tikur Anbassa hospital, Addis Ababa, the only comprehensive cancer treatment center in Ethiopia.**

Main variables: **Prevalence of HIV, mean age, diagnosis of cervical cancer.**

Materials and methods: **All newly diagnosed, and biopsy proven uterine cervical cancer patients who were managed at Tikur Anbassa hospital records were sought. The records were identified perused and those found to fulfil study entry criteria were evaluated and information collected using structured questionnaire. Data required from each study subject included; socio-demographic, reproductive characteristics and clinical information. Data was then pooled, screened and entered in SPSS. The results were computed and presented in the form of; tables and figures, mean with standard deviation and proportion for quantitative and qualitative statistic respectively. T-test for equality, Chi-square test, and logistic regression were used to measure associations. Significance level was set at P value of 0.05.**

Result: **Of the 255 subjects studied, majority has late clinical stage and squamous cell carcinoma histologically, 64.7% and 92.5% respectively. Similarly,34 out of the 255 were positive for HIV, making the overall sero-prevalence rate of 13.3%. The mean age of the total study population was 46 ±10.55 years. Significant difference was observed in the mean age of cervical cancer occurrence for HIV infected cases compared to the non-infected, 37.01 ± 6.7 and 48.23±10.26 years, respectively (p=000).**

HIV status and CD4 count were not shown to have any association with clinical stage and histologic variants. Having more than one lifetime sex partner and age less than 40 years were independently shown to have significant association with HIV sero-positivity. Mean CD4 count of the HIV positive subjects was 442.2±251.27.
Conclusion and recommendation: **In this study HIV infected women with cervical cancer were 8 to 14 years younger than HIV- negative women with cervical cancer. The disease stage and histology were not different in both groups, and without evidence of advanced disease in immune compromised state. It is recommending that further larger scale multicenter study, to explore the reasons for the younger age of occurrence of invasive cervical cancer in patients with HIV/AIDS.**

INTRODUCTION

Cervical cancer, a global public health problem, accounting for almost 300,000 deaths annually, is the second most common cancer among women worldwide (1). Globally, estimates in 2010 indicate that every year 493,243 women are diagnosed with cervical cancer and 273,505 of them die from the disease with the case fatality rate of 55% (2). Eight three percent of new cases and 85% of related deaths occur in resource-poor countries: where in many regions it is the most common cancer among women affecting the poor and vulnerable women at a time of life when they are critical to social and economic stability (3).

In Africa, the estimates indicate that every year 78,897 women are diagnosed and 61,671 die from the disease (4). According to the WHO estimates in Ethiopia, 7.600 new cases are diagnosed with cervical cancer and roughly 6,000 women die of the disease each year, making the case fatality rate of 79% (5).

Although there is no national cancer registry in Ethiopia, reports from a retrospective review of biopsy result, have shown that it is the most prevalent cancer among women. For instance, among 243 cancer cases at Gonder University hospital, Northwest Ethiopia, cervical cancer accounted for 12.8% of all cancers and 65.9% of female genital tract cancers [6]. Similar studies from Addis Ababa and Yirgalem Hospital, Southern Ethiopia, revealed that cervical cancer accounted for the major proportion of female malignancies accounting for 32% and 5.8% respectively (7, 8). A study done on 2,111 women attending hospitals and clinics in Addis Ababa has also reported that the prevalence of invasive cancer to be 15.6/1000 (9).

The joint United Nations Program on HIV\AIDS(UNAIDS) estimated that 40 million adults and children were living with HIV/AIDS at the end of 2003, with about 70% these individuals were confined to sub-Saharan Africa, where more than half of the infected people are women with very limited access to cervical cancer screening (10). In 2011, adult HIV AIDS prevalence in Ethiopia was estimated at 1.5 percent and approximately 1.2 million Ethiopians were living with HIVAIDS in 2010. Data from the 2011 EDHS indicate HIV/AIDS prevalence is higher among women than men, 1.9% and 1.0% respectively (11). The association between HIV and invasive cervical cancer is complex, with several studies demonstrating an increased risk of pre-invasive cervical lesions among HIV infected women (12). In addition several case control studies have demonstrated a 2 to 12 times higher cytological abnormality rates in HIV positive women against the controls, HIV sero-negative women (13, 14). The results of cytology and biopsy in HIV infected compared to uninfected women showed a significant difference both in 1ow grade squamous intraepithelial lesions (CIN 1) 13%, and 4% and high grade squamous intraepithelial lesions (CIN II and CIN

III),7% and 1% respectively (15). Even a higher rate of high-grade lesions observed in 273 HIV positive compared to 161 HIV negative women that is put at 42% and 8%, respectively (16). Several studies from Africa also support the strong and consistent relationship between co-infection with HIV and HPV and CIN (17, 18, 19). However, there have not been significantly higher incidence rates of invasive cervical cancer associated with the HIV epidemic.In1993, the US Centers for Disease Control (CDC) recorded 16,784 cases of women with AIDS and cervical cancer was the most common (1.3%) type of cancer diagnosed among these women (16). As a result, the CDC added invasive cervical cancer to its list of AIDS-defining illnesses which is also supported by other studies (20, 21).

Case reports observing a rapid progression to invasive cervical cancer in H1V-infected women have also been published (22, 23, 24). In the observational data from the Sentinel Hospital Surveillance System for HIV infection, the prevalence of invasive cervical cancer was modestly higher for HIV infected women compared to uninfected women of 10.4 cases per 1000 women and 6.2 cases per 1000 women respectively (25). In some African countries like Uganda, where HIV has been endemic for over a decade, several case control studies have found an association between HIV and invasive cervical cancer (26). In South Africa, relative risk of HIV with cervical cancer is found to be 1.6 (27). In Kenya, young women with invasive cervical cancer under 35 years of age were 2.6 times more likely to be HIV positive than controls of similar age (28). However, in Zimbabwe, no change in cervical cancer incidence has been demonstrated by the cancer registry (29). It is difficult to ascertain the actual incidence of cervical cancer in HIV infected women in HIV endemic countries where the burden of cervical cancer is highest, but cancer registries are still very scanty. Ethiopia is one of the countries where the magnitude of both HIV and cervical cancer is supposedly found to be high. The country has only one operational center at Tikur Anbassa hospital which is found in the capital city, Addis Ababa, where comprehensive cancer treatment is given. In addition to be the center for comprehensive cancer treatment, it is one of the centers in the country where HIV/AIDS prevention and treatment is provided. This study was designed to determine the prevalence of HIV among patients with histologically proven cervical cancer and describe the characteristics of patients with cervical cancer and HIV. It was not our primary intention to determine viral load in our study subjects with HIV/AIDS, as this test is not routinely performed in all public hospitals because of limited availability, and high cost if done in private institutions. The results of this study will lay a benchmark for planning interventions, such as selective screening and treatment of HIV infected women in places with limited resource and high magnitude of both HIV and cervical cancer.

MATERIALS AND METHODS

A facility-based cross-sectional descriptive study was conducted in women with histologically confirmed carcinoma of cervix in the outpatient department of Obstetrics and Gynecology, Tikur Anbassa Specialized Hospital, from June 1, 2013 to August 9, 2013.

Tikur Anbessa Specialized Teaching Hospital is the only central referral hospital and cancer diagnostic and treatment center in the capital of the country that provides services for patients coming referred or self-referred from all corners of the country. This referral hospital also serves as one of the centers in the country where HIV/AIDS prevention and treatment services are provided.

Study population: The study population were all women with biopsy proven cases of cervical cancer. These were either newly diagnosed at the study site or referred to the study site for the first time with cervical cancer. Sample size calculation for single proportion was made using the 21% prevalence of HIV in cervical cancer patients in Tanzania. The sample size calculated with the above assumption was 255.

All women with invasive cervical cancer who visited the study site during the study period who were fit for the interview and consented to be interviewed were enrolled consecutively till the desired sample size was achieved. All biopsy proven invasive cervical cancer cases were clinically staged by the senior obstetrician and gynecologist working at gynecology oncology referral clinic. In addition, all invasive cervical cancer patients were made to undergo provider initiative counseling and testing for HIV as part of regular work up as per the national HIV testing algorithm (30), unless their status is known and documented before.

Data was collected by the practicing residents using a structured questionnaire on socio-demographic and reproductive characteristics. The study participants were interviewed at the exit after completing their clinic visit. The clinical records of the study participants were reviewed for the details of the clinical information. Training was given to data collectors on the objective of the study, confidentiality of information, respondent's right, informed consent, and techniques of the interview.

Data was entered, cleaned and errors related to inconsistency of data were checked and corrected and analyzed using SPSS version 20.0 statistical software. Continuous variables were summarized using mean with standard deviation. Categorical variables were summarized into frequencies and percentages and presented in descriptive and tabular forms. Differences between means were tested by t-test. The Chi-square test was used to compare categorical variables.

Ethical clearance was obtained from Department's Research and Publication Committee. All the study participants were reassured that they would be anonymous. Names or any personal identifiers were not recorded. Respondents were clearly told about the study and the variety of information needed from them. They were given the chance to inquire anything related to the study and made free to decline or stop the interview at any moment they want if that was their choice. Informed written consent was obtained from all study participants.

RESULT

All the two hundred fifty-five subjects were studied. The age characteristics; range from 22-72years, and mean age of 46 ±10.6 years. Eighty-nine (34.9%) and 69(27%) of the study subjects fell in the age category of 40-49 and 50-59 years, respectively. Only 9(3.5%) of the subjects were in the age category below 30 years of age (Table1).

Eighty-two percent of our study subjects were from the three regions of the country namely, Oromia 82(32.2%), Addis Ababa 73 (28.6%) and Amhara 73 (28.65%). The majority of the respondents were Amhara in ethnicity accounting for 119 (46.7%) followed by Oromo 92 (36.1%); and most were housewives followed by government employee by occupation numbering 142 (55.7%) and 82(32.2%), respectively. Three fourth, 175 (69.8%) of the participants were Orthodox Christian by religion followed by Muslims 48(18.8%). and most 191 (75%) were married and 161(63.3%) were illiterate (Table 1).

That more than half, 158 (62%) of the participants had parity more than four with mean parity of 5.55±3.15. One hundred fifty-four (60.4%), had more than one sexual

partner in their lifetime with mean lifetime sexual partner of 1.93 ±1.31. The age at first sexual intercourse ranges from 12- 28 years, with the mean age of 16.40±2.9 years.HIV infected cervical cancer patients had lower parity, higher age at first sexual intercourse and higher number of lifetime sexual partners than HIV non- infected cervical cancer patients with the mean parity of 4.11±2.37 and 6.11±3.18. The mean age at first sexual intercourse of 17.71±3.89 and 16.20±2.67 and the mean lifetime sexual partners of 2.24±1.56 and 1.88±I.33 for HIV infected and non-infected in their respective orders. When these were compared for equality of means using t-test, significant difference was observed for parity and age at first sexual intercourse with p=0.00 and p=0.005 respectively, while the difference was not significant for lifetime number of sexual partners, P=0.144 (Table 5).

Out of the 255 subjects screened for HIV, 34 were found to be positive for HIV, giving a sero-prevalence of 13.3%. There is a statistically significant difference in the mean age of HIV infected compared to the non- infected. 37.09±6.71 versus 48.23±10.26 respectively p=000. Most of the HIV positive patients were in the age group of 30 to 39 and 40-49 years, 14(41.2%) in each group, whereas the majority of patients who were HIV negative were in the 40-49 and 50-59 years accounting for 75 (33.9%) and 68 (30.8%), respectively. Among the HIV negative 40(16.7%) were more than 60 years, while only one patient among HIV positive was more than 50 years, and the HIV positive being about 11 years younger than HIV negative (Table 2, Figure 1).

The majority the study subjects as shown in Table 3 and Figure 2, 165 (64.7%) were at a late stage of cervical cancer at presentation (stage IIB and above) and squamous cell carcinoma was the most common histopathologic diagnosis accounting for 246 (92.5%) of the respondents and the rest 9 (7.5%) diagnosed as adenocarcinomas.

Of the HIV positive patients, 32(94.1%) had their CD4 cell count per cubic millimeter determined, that showed the mean CD4 count of 442.19 ± 251.27, and 27(84.4%) of the HIV positives had CD4 count of greater than or equal to 200 cells/mm^3. There was no association between CD4 count and FIGO clinical stage at presentation (Chi-square 0.995, p =0.617), (Table 4). Similarly, HIV status has no association with clinical stage at presentation and histologic diagnosis with Chi-square1.337 and 0.107, p=0.247 and 0.743, respectively as shown in (Table 3).

Factors associated with HIV sero-positivity were explored in a binary logistic regression analysis. Having more than one lifetime sex partner and age less than 40 years were significantly associated with HIV sero-positivity (Table 6).

Table 1

Socio demographic characteristics of the study subjects

Characteristics		Frequency	%
	<30	9	3.5%
	30-39	51	20.0%
Age	40-49	89	43.9%
	50.59	69	27.1%
	>60	37	14.5%
	Mean	46.75+10.55	
Marital status	Married	191	74.9%
	Widow	30	11.8%
	Divorced	34	13.3%
Religion	Orthodox	178	69.8%
	Muslim	48	18.8%
	Protestant	29	11.4%
Education status	Illiterate	161	63.1%
	Read and write	52	20.4%
	Elementary	14	5.5%
	High school and above	28	11.0%
Occupation	Government employed	26	10.2%
	Self employed	5	2.0%
	Farmer	82	32.2%
	Housewife	142	55.7%
Ethnicity	Amhara	119	46.7%
	Oromia	92	36.1%
	Tigre	15	5.9%
	Gurage	30	11.4%

Table 2

Age group of women with histologically confirmed cervical cancer by HIV status

Age in Years	HIV			p-value
	Negative	Positive	total	
<30	4(1.8%)	5(14.7%)	9(3.5%)	0.000
30-39	37(16.7%)	14(41.2%)	51(20%)	-
40-49	75(33.9%)	14(41.2%)	89(34.9%)	-
50-59	68(30.8%)	1(2.9%)	69(27.1%)	-
>60	37(16.7%)	----	37(14.5%)	-
Mean	48.23#10.23	37.10#6.71		-
Total	221(100%)	34(100%)	225(100%)	

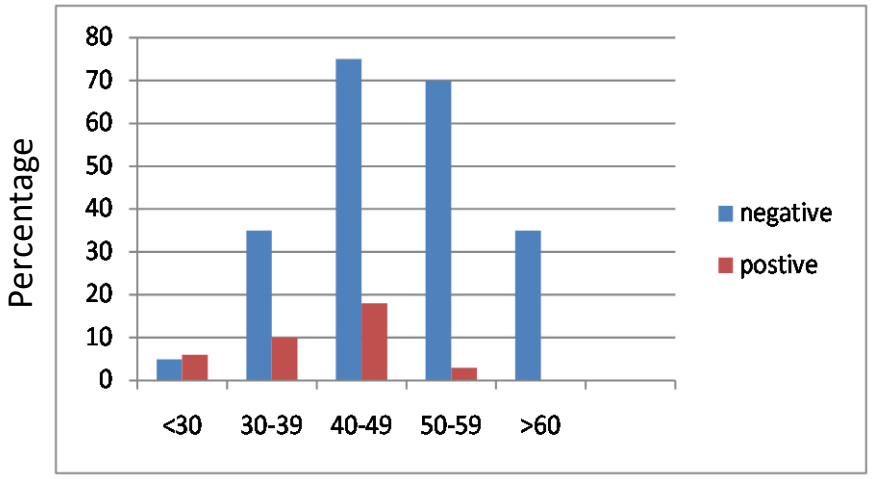


Figure1: Bar graph showing age group of women with histological confirmed cervical cancer by HIV status.

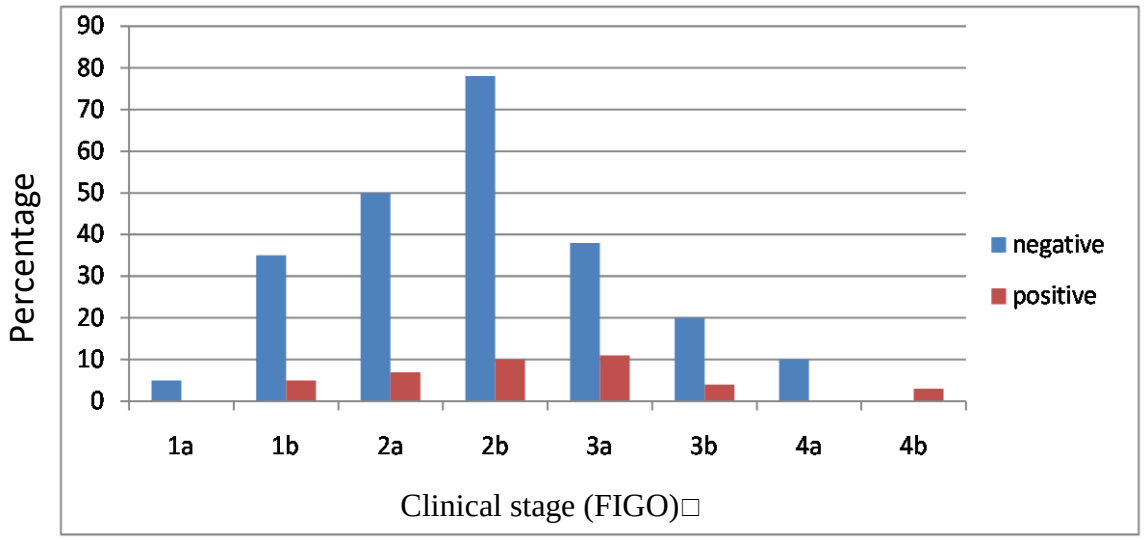
Table 3

Histological diagnosis and clinical stage of women with cervical cancer by HIV status

Characteristics		**HIV status**			**p-value**
		Negative	**Positive**	**Total**	
Clinical stages at Presentation	Early stage□ Late stage□□ total	81(36.7%) 140(63.3%) 221(100.0)	9(26.5%) 25(73.5%) 34(100.0%)	90(35.3%) 165(64.7%) 255(100.0%)	0.247
Histological diagnosis	Squamous cell Adenocarcinoma	205(92.8%) 16(7.2%)	31(91.2%) 3(8.8%)	236(92.5%) 19(7.5%)	0.743
Total		**221(100%)**	**34(100.00%)**	**255(100.00%)**	

□Early stage: stage <=IIa

□□Late stage: stage >=IIb



FIGO: International Federation of Gynecology and Obstetrics

Figure 2: Bar graph showing percentage distribution of clinical stage at presentation of women with histologically confirmed cervical cancer by HIV status.

Table 4

Clinical stage at presentation of HIV positive subjects by CD4 cell count

CD4 cell count /mm3 within last six months	**Clinical stage at presentation**			
	Early stage □	**Late stage □□**	**Total**	**P-value**
<200	1(11.1%)	4(16.0%)	5(14.7%)	0.617
≥200	8(88.9%)	19(76.0%)	27(79.4%)	
Unknown	-	2(8.0%)	2(5.9%)	
Total	9(100.0%)	25(100%)	34(100%)	

□Early stage: <=IIa

□□Late stage: >=IIb

Table 5

Characteristics of women with historically confirmed cervical cancer by HIV status

Characteristics	HIV Status		Total	
	Negative N=221	Positive N=34		P-value
Parity				
<5	74(33.5%)	23(67.6%)	97(38.0%)	0.00
≥5	147(66.5%)	11(32.6%)	158(62.0%)	
Mean	6.12± 3.18	4.12± 2.37	4.12± 2.37	
Median	6(IQR=4)	4(IQR=2.25)		
Age at first sexual intercourse				
<16	119(53.8%)	11(32.4%)	130(51.0%)	0.005
≥16	102(46.2%)	23(67.6%)	125(49%)	
Mean	16.2± 2.67	17.71± 3.89		
Median	15(IQR=3)	18(IQR=5)		
Lifetime number of sexual partners				
<1	94(42.5%)	7(20.6%)	101(39.6%)	0.144
≥1	127(57.5%)	27(79.4%)	154(60.4%)	
Mean	1.88± 1.33	2.24± 1.66		
Median	2(IQR=1)	2(IQR=0.25)		

Table 6

Binary logistic regression analysis of selected patient characteristics in women with histologically confirmed cervical cancer by HIV status

Risk factor	HIV Negative N=221	HIV Positive N=34	Total (%)	Adjusted OR	95% CI	P-value
Party ≥5	147(66.5%)	11(32.4%)	158(62%)	0.437	0.182-1.03	0.065
Life time sexual partners ≥1	127(57.5%)	27(79.4%)	154(60.4%)	3.159	1.259-7.928	0.014
Age at first sexual intercourse <16	119(53.8%)	11(32.4%)	130(51.0%)	1.806	.780-4.180	0.167
Age <40	41(18.6%)	19(55.9%)	60(23.5%)	3.51	1.452-8.484	0.005

DISCUSSION

The HIV sero-prevalence among cervical cancer patients in this study was 13.3%, higher than the prevalence in the general population and the antenatal clinics of Ethiopia of 1.9% and 3% respectively. This observation suggests that HIV could have a role in the pathogenesis of cervical cancer, or HIV and cervical cancer might share the same risk factors (11, 31).

The reported prevalence of HIV in cervical cancer patients in our study is similar to the report from Kenya and Cote d'Ivoire, 15% and 16.7% respectively (28,32) higher than the reports from Nigeria, South Africa, and China with rates of 2.7%, 7.2% and 1.6% in their respective orders (32, 33, 35) but lower than the 19% report among American women, and 21% from Natal of South African and Tanzania (35,36,38).These differences among various studies could be explained by differences in HIV sero-prevalence in the general population, specific population studied, or possibly reflecting the competing risk of dying from other HIV related conditions, as shown by the two South African studies of HIV sero-prevalence 32.5% in KwaZulu-Natal and 23.9% in Gauteng province (34).

The mean age of the study subjects of 46 years observed in our study is similar to the previous studies from Tikur Anbessa Hospital of which the mean age was 48 years (39,40). Similar findings were reported from Kenya and Cote d'ivore regarding the mean age of invasive cervical cancer patients,47and 46 years respectively (32,38).

Statistically significant difference was observed in our study in the mean ages of the HIV-negative patients compared to HIV-positive counterparts,48.23±I0.26 and 37.09 ±6.71 respectively, p=0.000, with H1V-infected women being about 11 years younger than HIV-non infected women. The result of our study is consistent with the number of other research findings where HIV infected women with cervical cancer are younger than HIV negative counterparts (28, 36, 41). The possible explanation for such differences could be: (1) HIV infection may shorten the progression from premalignant cervical lesions to ICC resulting in earlier presentation; (2) Women who have earlier more frequent sexual activity with multiple partners are at risk for both HPV and HIV, thus accounting for the younger age at presentation and (3) Higher HIV sero-prevalence rate among young women.

The result of our study has shown that HIV infected cervical cancer patients were shown to have low parity, older age at first sexual intercourse , and greater number of life time sexual partners compared to HIV non-infected cervical cancer patients with the mean parity of 4.1I+2.37 and 6.12+3.18,the mean age at first sexual intercourse of 17.71±3.89 and 16.20±2.67 and the mean life time sexual partners of 2.24±1.56 and 1.88±1.33 for HIV infected and non-infected respectively, and the difference was statistically significant(p= 0.00). These findings indicate that the effect of high parity and early age at sexual intercourse as a risk factor for cervical cancer seem to be diluted in HIV positive patients, probably reflecting HIV infection as a separate and significant risk factor for cervical cancer. The findings in our study were similar to a study done in South Africa where mean age at first sexual debut and the lifetime sexual partners show significant difference for HIV positive and negative patients (34).

Parity, the age at first sexual intercourse, lifetime number of sex partners, and the age of patient were explored in a binary logistic regression analysis for HIV sero-positivity. Having more than one lifetime sex partner and age less than 40 years were significantly associated with HIV sero positivity, p=0.014 and 0.00 respectively. This suggests that patients with cervical cancer and HIV infection have multiple sexual partners as a

common risk factor for the increase in the prevalence of HIV among cervical cancer patients may be from the indirect effect of multiple sexual partners resulting higher HPV and HIV infection.

The majority of patients in our study irrespective of the HIV status, were more likely to have late stage disease at diagnosis with25(73.5%) of HIV positives and 140(63.3 %) of HIV negatives. This may reflect that in places like ours where screening and preventive services are not developed, women may seek treatment only when they have advanced disease. Our finding is consistent with studies done in Cote d'Ivoire, Kenya and Tanzania (28, 33). But studies done in USA reported that HIV positive cervical cancer patients have a more advanced stage than HIV negatives (36). This difference could possibly be explained by the difference in the population studied, screening practices and the methodology used.

Nearly 80% of the HIV positives cervical cancer patients in our study had CD4 count above 200 cells/mm3, with mean count of 442±25.This suggests that HIV positive cervical cancer patients in this study are not as severely immune compromised as the report from South Africa, mean CD4 count 316 cells /µl (37) and report from USA, mean CD4 cell count 208 cells/µl (42). Also, from another North American study HIV infected women with CD4 count <200 have 7.7 times risk of having invasive cervical cancer (43). The disparity reflects the fact that cervical cancer among HIV-infected women in our set up may not reflect the presence of an AIDS-defining illness, but rather the high prevalence of cervical cancer in the background of an HIV epidemic. In addition, it may also be because, in our set up, women with HIV and cervical cancer in the presence of severe immune suppression associated with HIV infection could die of other opportunistic infection before presenting to health facilities. The finding in our study that squamous cell carcinoma was the commonest histologic type irrespective of the HIV status is consistent with many other studies (34, 36, 37, 44).

LIMITATIONS

The findings may not be extrapolated to the pattern of distribution of the diseases for the whole country as the participants represented only those who sought care at the health institution. Early death of HIV-infected women before they come to hospital due to other HIV related opportunistic infections could have resulted in underestimating the HIV sero-prevalence. This study did not separately assess HIV positive patients with regards to antiretroviral status.

CONCLUSION AND RECOMMENDATION

In is noted in this study that the younger age of occurrence of invasive cervical cancer in patients with HIV/AIDS compared to HIV negative women, thereby, impacting the future direction of care in women who are HIV positive in terms of cervical cancer prevention and control in the country.

Further a larger multicenter study is recommended to explore factors contributing for an early age of occurrence of cervical cancer in HIV infected patients. We recommend early initiation of screening of HIV positive women for premalignant cervical lesions as part of HIV/AIDS routine care, especially in resource limited setting where universal screening is not available.

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