

ORIGINAL ARTICLES

Prevalence and severity of cervical squamous intraepithelial lesion in a tertiary hospital in northern Tanzania

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Abstract: Cervical cancer is the second most common cancer in women worldwide and the leading cause of cancer deaths in Tanzanian women. Prevention of cervical cancer relies on the detection and treatment of Squamous Intraepithelial Lesion (SIL), a premalignant disease stage. Worldwide there are overwhelming reports associating SIL and HIV infection, however in Tanzania such reports are limited. A cross-sectional hospital-based descriptive study was conducted to determine the prevalence and severity of SIL in 234 HIV seropositive and seronegative women aged 18-68 years old at Kilimanjaro Christian Medical Centre in northern Tanzania. A structured questionnaire was used to collect sociodemographic data. In addition, blood was collected for rapid HIV antibody testing and CD4+ T-lymphocyte counts to associate with prevalence and severity of SIL from the cervical smear collections. A total of 214 subjects had smear results regarded as valid for interpretation, of which 46.3% were HIV seropositive. Overall rate of SIL was 17%. Proportion of SIL among HIV seropositive subjects was 32% versus 4% in seronegative subjects (OR=13.3, 95% CI=4.2-46.4). Low CD4+ T-lymphocyte cell count was associated with higher prevalence of SIL ($P=0.001$). The relationship between CD4+ T-lymphocyte cell counts and the severity of cervical SIL was significant ($P=0.007$). Marital status and number of lifetime sex partners were risk factors significantly associated with SIL ($P=0.004$ and 0.005 , respectively). SIL was not associated with age, education level, parity or age at sex debut. The prevalence and severity of cervical SIL was significantly associated with HIV infection and immunologic disease progression. These findings underscore the need for HIV screening among women with SIL, and the need for cervical cancer screening in HIV-infected women. Marital status and number of lifetime sex partners were significant risk factors associated with SIL.

Key words: HIV, cervical cancer, squamous intraepithelial lesion, risk factors, Tanzania

Introduction

Cervical cancer remains the second most common cancer in women worldwide with 493,000 new diagnoses and 274,000 deaths occurring each year. Eighty percent of these deaths occur among women from developing countries (Parkin *et al.*, 2002). In Tanzania the annual crude incidence rate of cervical cancer is 40.6 while crude mortality rate is 32.5 (WHO, 2009). In resource-rich countries, screening and treatment of pre-malignant cervical lesions is done on a regular basis, resulting in an 80% reduction in cervical cancer incidence and related mortality. In contrast, in resource-limited countries 60-80% of cases are diagnosed at an advanced stage of the disease with an accompanying poor prognosis (Parkin *et al.*, 2002; Sankaranayanan *et al.*, 2001).

Persistent infections with sexually transmitted oncogenic strains of human papilloma virus (HPV) such as types 16, 18 and 45 are central aetiological factors for the development of high grade squamous intraepithelial lesions (SIL) and cervical cancer worldwide (Bosch *et al.*, 1995; Franco *et al.*, 2001).

HIV seropositive women are at higher risk for SIL and cervical cancer compared to their seronegative counterparts (Palefsky *et al.*, 2001). Such factors account for higher proportions of preinvasive cervical neoplasia in HIV-infected than HIV-uninfected women worldwide (La Ruche *et al.*, 1998; Mandelblatt *et al.*, 1999; Massad 1999). Unlike other parts of the Africa, few study reports on the association between HIV infection and cervical SIL have been published in Tanzania (Mandelblatt *et al.*, 1999; Moodley *et al.*, 2006; Parham *et al.*, 2006). In West Africa, a study reported that high grade SIL was strongly associated with HIV-2 infection and not HIV-1 (Hawes *et al.*, 2003). In East Africa, one study in Tanzania reported no association between HIV infection and SIL (ter Muelen *et al.*, 1992); while another study investigating risk factors for SIL in HIV-infected women did not include HIV seronegative women as controls (Kapiga *et al.*, 1999).

Due to the contradictory results reported on the relationship between SIL and HIV serostatus in the previous Tanzanian studies (ter Meulen *et al.*, 1992; Kapiga *et al.*, 1999) and its impact on HIV / AIDS-related morbidity, this

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study was therefore conducted to re-examine this relationship. Specifically this study was carried out to determine the prevalence and severity of SIL and predisposing factors in HIV-infected women in relation to the degree of HIV disease progression.

Materials and Methods

Study area

This study was conducted at Kilimanjaro Christian Medical Centre (KCMC) in Moshi Tanzania. KCMC is one of the four teaching and referral hospitals in Tanzania. The hospital has 450 bed capacities and caters to residents of northern parts of Tanzania. Department of Obstetrics and Gynaecology runs Cervical Cancer Clinic (CCC) thrice a week. Most of the clients attending this clinic are women who come voluntarily to seek screening services and few referred patients from various other KCMC in- and out-patient departments.

Study subjects

A total of 234 women aged 18-68 years, with no prior history of total hysterectomy and willing to take HIV test and participate in the study were conveniently enrolled in the study from September 2006 to March 2007. Of these, 85 were women known to be HIV seropositive referred from KCMC Infectious Diseases Clinic (IDC) and 149 were those with unknown HIV serostatus who came for Pap smear test at the KCMC-CCC.

Study design and data collection

This was a cross-sectional prospective descriptive study. A Kiswahili structured questionnaire was administered to study participants to collect information on socio-demographic characteristics, risk factors for SIL and cervical cancer. After HIV pre-test counselling by a trained nurse to women with unknown HIV serostatus, 10ml of venous blood was collected to determine HIV antibody status using both Capillus and Determine HIV1/2 test kits. Samples from HIV seropositive women were sent for CD4+ T-Lymphocyte count measurement using a FACS Count Flow Cytometer (Becton Dickinson Biosciences). Cervical smears were collected using both wooden Ayres spatula and endocervical brush techniques from all subjects. The cells were transferred to the dry glass slide, fixed using 50% alcohol, and sent to the KCMC Pathology Department for staining and interpretation. These procedures were performed by a trained cytotechnician, and

interpretations were performed by a single Consultant Pathologist who was blinded to the subjects' HIV serostatus. Pap smear results were graded according to Bethesda system of cervical cytology interpretation (Solomon *et al.*, 2002); with the categories of normal smear, low grade and high grade SIL.

Data analysis

Data collected was entered and analysed using Statistical Package for Social Science (SPSS) version 12. Numerical variables were summarized into tables and charts while categorical variables were compared among women with or without outcome of interest using Chi-square test at 95% confidence level. Two sided p-value was used to assess level of significance.

Ethical consideration

Ethical clearance was obtained from KCMC Research Ethics Committee before beginning of the study. The purpose of the study, procedures to be taken and any untoward effects were thoroughly explained to the subjects whom were only enrolled post signing informed consent forms. Women who opted not to participate in the study received the equivalent care to study participants according to the KCMC therapy guidelines. To insure confidentiality hospital registration number and unique study number were used instead of names while study documents and data were kept in the locker accessible to research team only. Password known to research team was used to access all research electronic data.

Results

Socio-demographic characteristics

The mean age \pm SD of 234 women recruited in the study was 35 ± 9 years. About three quarters (73.1%) were married/co-habiting and only 4.7% divorced. Majority of the women, 72.2% had primary school education and only 2.6% had no formal education. Of 234 women, 65.4% were para 1 to 3 and only 2.1% were nulliparous; mean parity of women was 3 (range, 2-10). More than 45% had their sex debut at the age between 15 and 18 years; mean age at sex debut was 19 ± 3.7 years. Most women (90.6%) had 1 to 3 lifetime sexual partners with only 9.4% having 4 or more partners; mean number of lifetime sexual partners was 2 (range, 1-10). Majority of women, 67.5% mentioned that their partners had only one sexual partner while 2.6% had 4 or more sexual partners (Table 1).

Table 1: Socio - demographic characteristics of women enrolled in the study (N= 234)

Variable	Response	Frequency	Percent
<i>Age group (years)</i>	18-25	29	12.4
	26-35	90	38.5
	36-49	100	42.7
	≥50	15	6.4
<i>Marital status</i>	Single	23	9.8
	Married/co-habiting	171	73.1
	Widowed	29	12.4
	Divorced	11	4.7
<i>Educational level</i>	Non formal Education	6	2.6
	Primary	169	72.2
	Secondary	44	18.8
	Post-secondary	15	6.4
<i>Parity</i>	Nulliparous	5	2.1
	1 – 3	153	65.4
	4 – 5	52	22.2
	Above 5	24	10.3
<i>Age at sex debut (years)</i>	Less than 15	8	3.4
	15 – 18	108	46.2
	19 – 24	94	40.2
	≥25	24	10.3
<i>No. life time sex partners</i>	1	107	45.7
	2 -3	105	44.9
	≥4	22	9.4
<i>No. of partners of your partner</i>	1	158	67.5
	2 -3	70	29.9
	≥4	6	2.6

Of the 234 women, 103 (44%) were HIV seropositive. The median CD4+ T-lymphocyte count for HIV seropositive women was 304 cells/ μ L (IQR, 161-423). Age, marital status, age at sex debut, their number of lifetime sexual partners and the number of lifetime sexual partners of their male partners were significantly related to HIV serostatus. The chi-squared value for trend

analysis showed that women aged \geq 35 years, age at sex debut less than 18 years, widowed and multiple lifetime sexual partners were the characteristics associated with being HIV seropositive. Married women and women with age at sex debut more than 18 years were less likely to be HIV-infected (Table 2).

Table 2: Demographic characteristics and HIV serostatus (n, 234)

Variable	Response	Total	HIV+ve No (%)	HIV-ve No (%)	P-value
<i>Age group (years)</i>	18-25	29	6 (20.7)	23 (79.3)	
	26-35	90	27 (30.0)	63 (70.0)	
	36-49	100	63 (63.0)	37 (37.0)	
	≥50	15	7 (46.7)	8 (53.3)	<0.001
<i>Marital status</i>	Single	23	18 (78.3)	5 (21.7)	
	Married/co-habiting	171	49 (28.7)	122 (71.3)	
	Widowed	29	27 (93.1)	2 (6.9)	
	Divorced	11	9 (81.8)	2 (18.2)	<0.001
<i>Educational level</i>	None	6	4 (66.7)	2 (33.3)	
	Primary	169	72 (42.6)	97 (57.4)	
	Secondary	44	20 (45.5)	24 (54.5)	
	Post-secondary	15	7 (46.7)	8 (53.3)	0.69
<i>Parity</i>	Nulliparous	5	4 (80.0)	1 (20.0)	
	1 – 3	153	64 (41.8)	89 (58.2)	
	4 – 5	52	22 (42.3)	30 (57.7)	
	> 5	24	13 (54.2)	11 (45.8)	0.263
<i>Age at sex debut (years)</i>	<15	8	5 (62.5)	3 (37.5)	
	15 – 18	108	54 (50.0)	54 (50.0)	
	19 – 24	94	40 (42.6)	54 (57.4)	
	≥25	24	4 (16.7)	20 (83.3)	0.018
<i>No. of life time sex partners</i>	1	107	28 (26.2)	79 (73.8)	
	2-3	105	59 (56.2)	46 (43.8)	
	≥4	22	16 (72.7)	6 (27.3)	<0.001
<i>No. of partners of your partner</i>	1	158	55 (34.8)	103 (65.2)	
	2-3	70	45 (64.3)	25 (35.7)	
	≥4	6	3 (50.0)	3 (50.0)	<0.001

Prevalence of SIL in HIV-infected and HIV-uninfected women

Among 234 women, 214 (91.5%) had Pap smear results available for interpretation. Of these 214 subjects, 99 were HIV seropositive (46.3%). Overall 36 women had SIL, of which 32 were HIV seropositive (88.9%). The proportion of

SIL among HIV seropositive women was 32.3% (32/99) and 3.5% (4/115) for seronegative women (OR= 13.3; 95% CI 4.2-46.4). Pap smear results according to Bethesda classification indicate that 178 (83%) of the women were normal. Women with low and high grade lesion were 21 (10%) and 15 (7%), respectively.

Table 3: Relationship between rate of SIL and degree of HIV progression according to CD4+ T- lymphocyte count (cells/ μ L)

Variable	Total	PAP smear results		Chi-square	P-value
		SIL No. (%)	Normal No. (%)		
CD4+ T lymphocyte cell count					
<200	31	18 (58.1)	13 (41.9)		
200-499	49	11 (22.4)	38 (77.6)		
≥500	19	3 (15.8)	16 (84.2)	13.9	0.001

Relationship between prevalence and severity of SIL and HIV progression

The prevalence of SIL was higher (58.1%) in subjects with a CD4+T-lymphocyte count below 200 cells/ μ L compared to 22.4% with 200-499 cells/ μ L and 15.8% in subjects with counts above 500cells/ μ L. This difference was highly significant ($P=0.001$) (Table 3). In HIV seropositive women with SIL, 37.5% (12/32) had high grade SIL, and 58.3% (7/12) of these women with high grade SIL had CD4+ T lymphocyte counts below 200cells/ μ L. In comparison, only 8.3% (1/12) of HIV-infected women with CD4+ T-lymphocyte counts above 500 cells/ μ L had high grade SIL ($P=0.007$) (Table 4).

Association between socio-demographic characteristics and rate of SIL

Among 214 women with valid Pap smear results, marital status and number of life time sexual partners were significant risk factors for the development of SIL (marital status- $P=0.004$; number of life partners- $P=0.0049$). Divorced women had more SIL 36.4% (4/11), followed by single women 31.8% (7/22), widowed 29.6% (8/27) and married/co-habiting group 11% (17/154) ($P=0.004$). Women with multiple life time sexual partners had higher rate of SIL (23.1% vs. 8.6%) than women who had one life sexual partner ($P=0.0049$). There was no significant association between development of cervical SIL and age, education level, parity and age at sex debut (Table 5).

Table 4: Relationship between degree of SIL and degree of HIV progression (N=99)

CD4+ T-Count (cells/ μ L)	Total	PAP smear results			Chi-square	P-value
		HGL	LGL	Normal		
		No. (%)	No. (%)	No. (%)		
<200	31	7 (22.6)	11 (35.5)	13 (41.9)		
200 – 499	49	4 (8.2)	7 (14.3)	38 (77.6)		
\geq 500	19	1 (5.3)	2 (10.5)	16 (84.2)	14.0	0.007

Note: PAP= Papanicolous; HGL= High grade squamous intraepithelial lesion; LGL= Low grade squamous intraepithelial lesion

Table 5: Relationship between various social demographic characteristics and rate of cervical dysplasia (N=214)

Variable	Response	Total	PAP results		Chi-square	P-value
			SIL	Normal		
			No. (%)	No (%)		
<i>Age group (years)</i>	18-25	29	2 (6.9)	27 (93.1)	7.1	0.07
	26-35	82	10 (12.2)	72(87.8)		
	36-49	90	22 (24.4)	68(75.6)		
	\geq 50	13	2 (15.4)	11 (84.6)		
<i>Marital status:</i>	Single	22	7 (31.8)	15 (68.2)	13.4	0.004
	Married/co-habiting	154	17 (11.0)	137 (89.0)		
	Widowed	27	8 (29.6)	19 (70.4)		
	Divorced	11	4 (36.4)	7 (63.6)		
<i>Educational level</i>	None	5	2 (40.0)	3 (60.0)	3.4	0.33
	Primary	157	28 (17.8)	129 (82.2)		
	Secondary	37	5 (13.5)	32 (86.5)		
	Post-secondary	15	1 (6.7)	14 (93.3)		
<i>Parity</i>	Nulliparous	5	1 (20.0)	4 (80.0)	2.1	0.545
	1 – 3	141	20 (14.2)	121 (85.8)		
	4 – 5	41	10 (24.4)	31 (75.6)		
	> 5	21	5 (23.8)	16 (76.2)		
<i>Age at sex debut (years)</i>	<15	6	2 (33.3)	4 (66.7)	2.7	0.448
	15 – 18	104	19 (18.3)	85 (81.7)		
	19 – 24	88	14 (15.6)	74 (84.1)		
	\geq 25	16	1 (6.3)	15 (93.8)		
<i>No. of life time sex partners</i>	1	93	8 (8.6)	85 (91.4)	7.9	0.0049
	\geq 2	121	28 (23.1)	93 (76.9)		

Discussion

Overall rate of SIL by a single Pap smear test in this study population was 17%. However most of subjects with SIL (88.9%) were significantly detected among HIV seropositive women. These results are consistent with other study reports elsewhere (Massad 1999; Moodley *et al.*, 2006; Parham *et al.*, 2006), however they differ from those reported in the study done in Dar es Salaam, Tanzania which showed that HIV serostatus was not significantly associated with SIL (Meulen *et al.* 1992). This could have happened due to a number of reasons. The difference in the mean age in these two study populations, with the previous study having a lower mean age of HIV seropositive women (27.1 vs. 38.6 years). This may be related to the duration needed for development of SIL from the day of HPV and HIV infections. Enrolling women admitted to the ward due to different reasons such as pelvic inflammatory diseases and infertility, the group which may have a higher prevalence of sexually transmitted infections and cervicitis leading to the under detection of SIL from vagina discharges. In contrary, our study population involved women coming for a baseline Pap smear from IDC and the community without any gynaecological complaints. While the study by Meulen and colleagues included mostly asymptomatic HIV cases, our study enrolled mostly symptomatic HIV-infected women with a median CD4+ T-lymphocyte count of 319 cells/ μ L, which is likely to have increased the likelihood of SIL.

Low CD4+ T lymphocyte cell counts significantly increased the likelihood of having cervical SIL, with most of the lesions seen at CD4+ T Lymphocyte cell counts below 200cells/ μ L. This is in agreement with most reports on rate of cervical SIL and HIV infection (Wright *et al.*, 1994; Massad, 1999), possibly due to reactivation and persistent infection with the higher risky HPV such as type 16 and 18 (Wright *et al.*, 1994; Palefsky *et al.*, 2001). The significant statistical difference between the degree of immunosuppression (by CD4+ T-lymphocyte cell counts) and the degree of cervical SIL shows that the more the immunity is suppressed the higher the likelihood of having high grade cervical SIL. The results are consistent with those reported in other studies (Hawes *et al.*, 2003; Parham *et al.*, 2006).

Cervical SIL was significantly more likely to be observed in single women (not

married, divorced, widowed) than women with permanent partners (married/cohabiting). Single women were likely to have multiple partners, a factor which was also seen to be significantly associated with SIL. This group was also seen to have a higher rate of HIV infection compared to married/cohabiting women). Multiple partners and HIV infection are factors highly associated with higher rates HPV infections, persistence and progression to SIL (Palefsky *et al.*, 2001; Massad, 1999). A similar trend, however insignificant was seen with single/widowed developing HGL compared to married women in a West African study (La Ruche *et al.*, 1998). Despite the significant association between SIL and number of life time partners noted in our study, a report in Dar es Salaam, Tanzania could not find this association (Kapiga *et al.*, 1999). It is possible that, the difference in study populations accounted for this as the Dar es Salaam study dealt only with HIV seropositive women whom might have more or less same sex characteristics compared to this study with both HIV seropositive and seronegative women. Like in the study in Dar es Salaam (Kapiga *et al.*, 1999), age was not significantly associated with cervical SIL. However, women within 36-49 years had a higher proportion of SIL (24.4%), in comparison to other age groups. In contrast, a study in USA (Wright *et al.*, 1994) reported cervical SIL to be significantly associated with age, and mainly beyond 35 years. The difference could have been attributed by the smaller sample size in our study population. As with the other studies in Tanzania, education level and age at sex debut was not associated with SIL (Kapiga *et al.*, 1999).

In conclusion SIL is highly prevalent in symptomatic HIV infected women in northern Tanzania and therefore it is of critical importance to initiate regular cervical cancer screening programme services to at risk women in the population and especially HIV seropositive women attending centres for treatment and care in order to alleviate preventable causes of HIV/AIDS associated precancerous and cancer morbidities.

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Declaration of conflict of interest

The authors hereby declare to have no any competing interest.

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