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Observed Age Difference and Clinical Characteristics of Invasive Cervical Cancer Patients in Tanzania; A Comparison between HIV-Positive and HIV-Negative Women

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Abstract

Objectives: Human Immunodeficiency Virus (HIV) infection may associate to invasive cervical cancer (ICC) disease course and outcome. However, there is inconsistency of data regarding to the presence of HIV infection in women with ICC from different geographical population groups. To study the current HIV association with ICC in Tanzania, we evaluated the presence of HIV infection in women diagnosed with ICC.

Methods: We conducted a hospital-based study of 152 women histologically diagnosed with ICC at the Ocean Road Cancer Institute, Tanzania for one year. Rapid antibody test was used to check for HIV infection status. Chi-square test and logistic regression were used for statistical analysis and the tests were considered significant if $p < 0.05$.

Results: HIV-positive women were significantly younger than HIV-seronegative women; the median age was 36 years (IQR 28-62), compared to 56 years (IQR 38-81), respectively, $p < 0.001$. In a stratified analysis, among HIV-positive women, 82% (22/27) were below age 40 years compared to only 13% (16/125) in women aged >40 years. In a pooled analysis, covariates of ICC with regard to HIV infection were, age at sexual debut below 16 years ($p < 0.001$) and low education level ($p = 0.001$). Moreover, statistical analysis revealed that treatment comorbidity, pre-treatment blood transfusion and low pretreatment white blood cell count were significantly associated with HIV-positive status ($p < 0.05$).

Conclusion: HIV-positive women were twenty years younger than HIV-seronegative women, both diagnosed with ICC ($p < 0.001$). A large population based case-control

study would advance our understanding on the temporality of this association.

Keywords: Invasive cervical cancer; HIV; Age difference; Clinical characteristics; Ocean road cancer institute

Introduction

Cervical cancer accounts for 528,000 new cases and 266,000 deaths worldwide each year, more than any other gynecologic cancer [1]. Among these deaths, 88% occurring in developing countries, especially in sub-Saharan Africa [2]. However, numerous studies suggest that HIV infection is associated with the rapid progression of high risk human papillomavirus (HR-HPV)-induced cervical premalignant lesions to invasive cervical cancer [2], and have shown that HIV-positive women have a higher prevalence of HR-HPV infection which is the causative organism for cervical cancer, than HIV-seronegative women [3].

Although sexual behavior is a recognized risk factor for both HIV and HPV infection acquisition, there is a huge evidence suggesting that HIV infection increases the risk of HPV acquisition [4]. Further, HIV infection with its subsequent immunosuppression favors persistent and recurrent HR-HPV infection [5]. On the other hand, in cervical cancer molecular genetics, it is believed that HPV infection may influence repeated mutations during HR-HPV DNA integration into host genomic DNA to enhance cervical carcinogenesis process [6].

Moreover, as currently, HIV infected women can live longer due to increased availability of antiretroviral therapy (ART), many retain a considerable risk of persistence infection with HR-HPV and a high possibility of progressing to invasive cervical cancer [7]. The incidence of cervical cancer has been changing worldwide, with increasing incidence in women below 40 years of age [8] which may highlight specific age-

cohort effects on morbidity and mortality probably due to the result of HR-HPV infection acquired at a younger age or due to the effect of HIV co-infection [2,8].

However, there is inconsistency of data regarding to the association of HIV and ICC from different geographical population groups [9]. For example, In Tanzania, although HIV infection has already been reported to be prevalent in women with invasive cervical cancer treated at the Gynecology department at the Ocean Road Cancer Institute, there is a lack of local data on the current existing presence and the impact of HIV infection in women diagnosed with ICC [10-12].

Our study therefore was undertaken to establish the following in this local cervical cancer population: HIV status at the age of cervical cancer diagnosis, cervical cancer characteristics and assessment of the outcome with regard to treatment options in HIV positive versus HIV negative women in Tanzania.

Methods

Sample size

We conducted a hospital-based prospective study with a convenient sample size of 152 women, histologically diagnosed with ICC at the Ocean Road Cancer Institute, Tanzania for a period of one year. Women were further grouped according to their age at cervical cancer diagnosis, disease stage and the HIV status.

Study population and study period

In order to avoid study selection bias, only newly diagnosed women with invasive cervical cancer at the gynecology department at Ocean Road Cancer Institute were recruited in the study from January 2014 to January 2015.

Variable selection

After obtaining ethical clearance and an informed consent from the study participants, extraction of information from original patients' files and log books at the hospital's medical records was done to access treatment details and outcomes. Missing data were excluded from the analysis.

Rapid antibody test was used to screen for HIV infection status using Tanzania HIV rapid test algorithm for detection of HIV antibodies as a standard operating procedure [12].

Statistical analysis

All data were entered into Microsoft Excel database and then transferred to the SPSS computer program version 22 (SPSS Inc. Chicago, Illinois) to create a working database. Chi-square test and logistic regression were used for statistical analysis. Fisher's exact test was considered in cells with number less than 5 and the test statistics were significant if $p < 0.05$.

Ethical clearance

The ethical clearance was requested and permission was sought from the management of the hospital. Confidentialities of participated women were highly considered.

Results

Out of 152 women diagnosed with invasive cervical cancer, only 2 women (1.3%) were disregarded in the analysis due to unknown HIV status. Twenty seven women (18%) were aged below 40 years and among HIV-positive women, 22 (81.5%) were under 40 years of age compared to 16 (13%) who were above 40 years. Furthermore, out of 123 women with invasive cervical cancer above 40 years, 107 (86%) were HIV-seronegative.

The median age for HIV-positive women with invasive cervical cancer was 36 years, IQR (28-62) years, while for HIV-seronegative women was 56 years, IQR (38-81) years, p -value < 0.001 (Figure 1). Furthermore, the age-group between 20-29 years old women with invasive cervical cancer were all HIV-positive. In addition, more than 80% of women with invasive cervical cancer who were above 49 years age-group were HIV-seronegative compared to less than 20% in HIV-positive women.

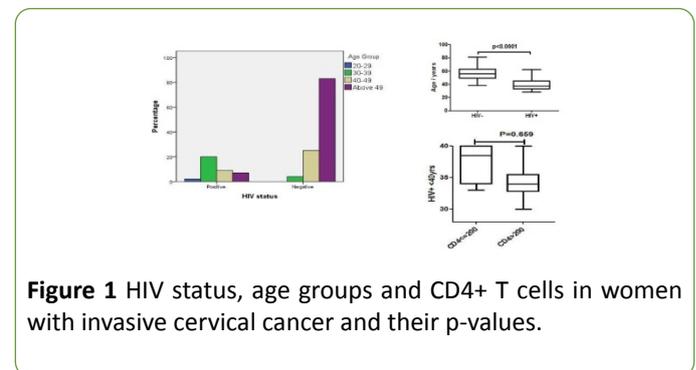


Figure 1 HIV status, age groups and CD4+ T cells in women with invasive cervical cancer and their p-values.

Covariates for HIV infection among women diagnosed with invasive cervical cancer were the age at sexual debut less than 16 years ($p < 0.001$) and low education level ($p = 0.001$). Furthermore, in multiple correlations analysis, there was a positive correlation between age of invasive cancer presentation and HIV positive status ($p < 0.001$) (Table 1).

In treatment modality, whether chemoradiation alone or surgery and chemo followed by chemoradiation, was not associated with HIV positive status ($p = 0.579$) (Table 2).

Discussion

To our best of knowledge, these findings are not only the first, but also add new evidence from a new study population on the involvement of HIV infection in ICC. In this study population of women with ICC in Tanzania, HIV seropositive women diagnosed with invasive cervical cancer were 20 years younger compared with HIV seronegative women. This affirms with the available and what is already known from the literature. Among women with ICC aged ≤ 40 years, 22/27

(81.5%) were HIV-positive compared to 16/123 (13%) in women aged >40 years. This shows and supports the fact that HIV-positive women may develop invasive cervical cancer at a younger age than HIV-seronegative women, $p < 0.001$ (**Figure 1**).

These findings reinforce the previous evidence and adding new results to the current existing similar findings. Our finding of 20 years age difference is among the highest results currently compared from recent similar studies done in sub-Saharan Africa. For example, in a study done in Botswana, participants with HIV infection were substantially 15 years younger than those without HIV infection (median, 42 years (IQR, 37 to 48 years) and 57 years (IQR 48 to 68 years), respectively) [13].

In addition, among HIV-infected women, the possible known risk of developing cervical cancer is 10 years earlier than in the general population, with a high rate of progression to an advanced disease stage with a poor treatment response and prognosis [14]. Another example, in a case-control study conducted in Ivory Coast, found that cervical cancer was associated with HIV infection for women under the age of 40 [8]. In another study done in Kenya, indicated that cases of patients younger than 35 years with cervical cancer were more likely to be HIV positive than HIV negative controls of similar age group [15], all these two findings are similar to our study.

In our study the median age in HIV positive women was 36 (28-62) while in HIV-seronegative women was 56 (38-81) (p -value < 0.001) (**Table 1**). This is the highest age difference so far. This could be due to the nature of other studies not to involve only women with invasive cervical cancer. For instance, Kafuruki et al. [14] found the median age for HIV-positive women was 32 years and 45 years for HIV-seronegative women, Mwakigonja et al. [16] found the median age of 34 years in HIV-positive women and 44 years in HIV-seronegative women while Balandya et al. [17] found the median age of 32 years in only in HIV-seropositive women.

In our findings, all women aged below 30 with ICC were HIV positive but not all women with ICC below age 40 were HIV positive either. Further, more than 80% of patients who were above the age 49 years were HIV-seronegative, however, there was a statistical significant difference in ages between HIV-positive and HIV-seronegative women, $p < 0.001$ (**Figure 1**). This finding supports the fact that HIV positive women may develop ICC at a younger age than HIV-seronegative women, although we agree that there might be a confounding effect of being sexually active due to younger age, which is a risk factor for HIV acquisition.

Furthermore, HIV positive women with ICC received more blood transfusion before ICC treatment and had low pretreatment hemoglobin levels compared to HIV-seronegative women, relative risks (1.83, 95% CI 1.07-3.14, $p = 0.029$). Therefore, all these findings in our study show the

burden and effects of HIV infection to ICC treatment course and outcome.

Table 1 Covariates of HIV infection with Pearson correlations and p-values.

Characteristics	HIV-Positive (%)	HIV-Negative (%)	Pearson Correlation, 0.01 level, 2-tailed	p-value
No. of participants	38	112	-	-
Median age (IQR), years	36 (28-62)	56 (38-81)	0.537	<0.001
Age at sexual debut	-	-	0.592	<0.001
≤ 16 years	29 (76.3)	15 (13.4)	-	-
≥ 16 years	9 (23.7)	97 (86.6)	-	-
Occupation				0.849
Employed	11 (28.9)	27 (24.1)	-	-
Unemployed	27 (71.1)	85 (75.9)	-	-
Education	-	-	0.036	0.001
Primary Education	School 26 (68.4)	51 (45.5)	-	-
Secondary education	school 11 (28.9)	36 (32.1)	-	-
No education	formal 1 (2.6)	25 (22.3)	-	-
Histology Diagnosis	at -	-	-	0.408
Squamous carcinoma	cell 35 (92.1)	109 (97.3)	-	-
Adenocarcinoma	3 (7.9)	1 (0.9)	-	-
Clear carcinoma	cell 0	1 (0.9)	-	-
Mucoepithelioid carcinoma	0	1 (0.9)	-	-
Cancer stage				0.387
IB	1 (2.6)	5 (4.5)	-	-
IIA	2 (5.3)	20 (17.9)	-	-
IIB	14 (36.8)	34 (30.4)	-	-
IIIA	17 (44.7)	40 (35.7)	-	-
IIIB	4 (10.5)	13 (11.6)	-	-
Recent CD4 count				
<200 cells/mL	8 (21.1)	-	-	-
>200 cells/mL	30 (78.9)	-	-	-

The strength of our investigation was that we carried out in women only diagnosed with ICC compared to other studies already done in Tanzania so far and specifically at a cancer institute. The weakness is that we were supposed at least to

involve age-matched healthy population as control in order to generate a proper comparison or to involve large sample size & other factors like duration of HAART use, viral load, and host genetic variations.

Table 2 Treatment modality or toxicity among cervical cancer patients with known HIV status.

Treatment or toxicity	HIV-positive (%) n=38	HIV-negative (%) n=112	Relative risk (95% CI)	p-value
Treatment modality				0.579
Chemoradiation alone	38 (100)	109 (97.3)	-	-
Surgery + Chemoradiation	0	3 (2.7)	-	-
Pretreatment BT				
Yes	19 (50)	34 (30.4)	Ref.	-
No	19 (50)	78 (69.6)	1.83 (1.07-3.14)	0.029
Pretreatment Hb levels				
Grade 0	34 (89.5)	108 (96.5)	Ref.	-
Grade 1	4 (10.5)	4 (3.5)	0.48 (0.23-1.02)	0.113
Post-treatment Hb levels				
Grade 0	21 (55.3)	95 (84.8)	Ref.	-
Grade 1	7 (18.4)	15 (13.4)	0.6 (0.28-1.17)	0.083
Grade 2	4 (10.5)	1 (0.9)	0.2 (0.13-0.41)	0.0064
Grade 3	4 (10.5)	1 (0.9)	0.2 (0.13-0.41)	0.0064
Grade 4	2 (5.3)	0	N/A	N/A
Pretreatment WBC				
Grade 0	30 (78.9)	101 (90.2)	Ref.	-
Grade 1	3 (7.9)	9 (8)	0.92 (0.33-2.56)	>0.99
Grade 2	5 (13.2)	0	N/A	N/A
Grade 3	0	2 (1.8)	N/A	N/A
Post-treatment WBC				
Grade 0	21 (55.3)	73 (65.2)	Ref.	-
Grade 1	10 (26.3)	18 (16.1)	0.63 (0.34-1.17)	0.215
Grade 2	5 (13.2)	11 (9.8)	0.71 (0.32-1.62)	0.525
Grade 3	1 (2.6)	8 (7.1)	2.02 (0.31-13.26)	0.68
Grade 4	1 (2.6)	2 (1.8)	0.67 (0.13-3.47)	0.542
Post-treatment toxicity				
Yes	35 (92.1)	109 (97.3)	Ref.	-
No	3 (7.9)	3 (2.7)	0.49 (0.21-1.14)	0.171

Conclusion

We are adding a new significant finding of twenty years age difference between HIV-positive and HIV-seronegative women presented with ICC ($p < 0.001$) from a new study population. More studies are needed to further investigate on the temporality of this association in order to advance our understanding of the disease. Other possible factors for ICC development such as HIV viral load, HIV/HPV co-infection,

duration of HAART use and most importantly the host genetics, should further be studied to improve our understanding of the disease. Therefore, in our study, we conclude and affirm to the literature that HIV-positive women develop ICC at a younger age compared to HIV-seronegative women.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, et al. (2015) Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 136: E359-386.
2. Chambuso RS, Shadrack S, Lidenge SJ, Mwakibete N, Medeiros RM (2017) Influence of HIV/AIDS on cervical cancer: A retrospective study from Tanzania. *J Glob Oncol* 3:72-78.
3. McDonald AC, Tergas AI, Kuhn L, Denny L, Wright TC Jr (2014) Distribution of human papillomavirus genotypes among HIV-positive and HIV-negative women in Cape Town, South Africa. *Front Oncol* 4:48.
4. Palefsky JM, Minkoff H, Kalish LA, Levine A, Sacks HS, et al. (1999) Cervicovaginal human papillomavirus infection in human immunodeficiency virus-1 (HIV)-positive and high-risk HIV-negative women. *J National Cancer Institute* 91: 226-236.
5. Ellerbrock TV, Chiasson MA, Bush TJ, Sun XW, Sawo D, et al. (2000) Incidence of cervical squamous intraepithelial lesions in HIV-infected women. *JAMA* 283: 1031-1037.
6. Diarra A, Botha MH (2017) Invasive cervical cancer and human immunodeficiency virus (HIV) infection at Tygerberg Academic Hospital in the period 2003-2007: Demographics and characteristics. *Southern Afr J Gynaecol Onco* 9: 1-5.
7. Kelly HA, Ngou J, Chikandiwa A, Sawadogo B, Gilham C, et al. (2017) Associations of Human Papillomavirus (HPV) genotypes with high-grade cervical neoplasia (CIN2+) in a cohort of women living with HIV in Burkina Faso and South Africa. *PloS one* 12: e0174117.
8. Adjorlolo-Johnson G, Unger ER, Boni-Ouattara E, Touré-Coulibaly K, Maurice C, et al. (2010) Assessing the relationship between HIV infection and cervical cancer in Côte d'Ivoire: A case-control study. *BMC Infect Dis* 10: 242.
9. CPG N (2006) The prevalence of HIV amongst women with cervix cancer. *SA Fam Pract* 48: 17.
10. Kahesa C, Mwaiselage J, Wabinga HR, Ngoma T, Kalyango JN (2008) Association between invasive cancer of the cervix and HIV-1 infection in Tanzania: the need for dual screening. *BMC public health* 8: 262.
11. <https://www.iedeaea.org/images/article/304/National%20Cervical%20Cancer%20Prevention%20Plan%20FINALFeb%202012.pdf>
12. Welfare TMOHaS (2011) Tanzania service delivery guidelines for cervical cancer prevention and control.
13. Dryden-Peterson S, Bvochora-Nsingo M, Suneja G, Efstathiou JA, Grover S, et al. (2016) hiv infection and survival among women with cervical cancer. *J Clin Oncol* 34: 3749-3757.
14. Kafuruki L, Rambau PF, Massinde A, Masalu N (2013) Prevalence and predictors of cervical intraepithelial neoplasia among HIV infected women at Bugando medical centre, Mwanza-Tanzania. *Infect Agent Cancer* 8: 45.
15. Gichangi PB, Bwayo J, Estambale B, De Vuyst H, Ojwang S, et al. (2003) Impact of HIV infection on invasive cervical cancer in Kenyan women. *Aids* 17: 1963-1968.
16. Mwakigonja A, Liset MT, Mwakyoma H (2012) Cervical cytological changes in HIV infected patients attending care and treatments clinic at Muhimbili National Hospital, Dar-Es-Salaam Tanzania. *Infect Agent Cancer* 15: 3.
17. Balandya BS, Pembe AB, Mwakyoma HA (2011) Cervical premalignant lesion in HIV infected women attending care and treatment centre in tertiary hospital Dar es Salaam. *East Afr J Public Health* 8: 185-189.