East African Medical Journal Vol. 97 No. 10 October 2020
IDENTIFYING THE RISK FACTORS FOR CERVICAL CANCER IN RWANDA: A CASE CONTROL STUDY

Charles Nkurunziza MD, MMed, MSc Master's student in Global Health Delivery, University of Global Health Equity, Rwanda; P.O.Box 5978 Kigali, Rwanda, Rex Wong DPT, MPH, MS, Associate Professor, Director, Bill and Joyce Cumming's Institute of Global Health, University of Global Health Equity, Rwanda; P.O.Box 6955 Kigali, Rwanda, Jenae Logan MSc, Director, Executive Education, University of Global Health Equity, Rwanda; P.O.Box 6955 Kigali, Rwanda, Diomede Ntasumbumuyange MD, MMed, Head of Department of Obstetrics and Gynecology, College of Medicine and Health Sciences, University of Rwanda; P.O.Box 3286 Kigali, Rwand, Ziad El-Khatib MSc, PhD, EMBA, Associate Professor , University of Global Health Equity, Rwanda, Department of Global Public Health, Karolinska Institutet, Stockholm, Sweden, World Health Program, Université du Québec en Abitibi-Témiscamingue (UQAT), Canada, P.O.Box 6955 Kigali, Rwanda

Corresponding author: Charles Nkurunziza, Master's student in Global Health Delivery
University of Global Health Equity, Rwanda. E-mail: nkurunziza86@gmail.com

IDENTIFYING THE RISK FACTORS FOR CERVICAL CANCER IN RWANDA: A CASE CONTROL STUDY

C. Nkurunziza, R. Wong, J. Logan, D. Ntasumbumuyange and Z. El-Khatib

ABSTRACT

***Background*: Identifying the risk factors for cervical cancer in a specific community informs the design of prevention programs adapted to the local context. Published such data are not available in Rwanda.**

***Objective*: This study aimed to describe the risk factors for cervical cancer in Rwanda.**

Design: Case control study

***Setting*: The study was conducted at the gynecologic oncology clinic of a University Teaching Hospital in Kigali.**

***Population*: Patients who attended the gyn-oncology clinic from January 2014 to December 2018.**

***Method*: Files of patients with histopathology-confirmed cervical cancer (cases) were matched with patients with no cervical cancer diagnosis (controls) by age (± 1 year) at a ratio of one to two and were examined for relevant information. Backward stepwise logistic regression was conducted to detect associations between risk factors and diagnosis of cervical cancer.**

***Results*: A total of 243 patient files were reviewed and 94.6% had no prior cervical cancer screening. The odds of cases having a secondary education were 0.15 times (OR=0.15, 95%CI: 0.04-0.058, p<0.01) the odds of the controls. The odds of cases being in moderate socioeconomic class were 0.37 times (OR=0.37, 95%CI: 0.17-0.82,**

p=0.01) compared to controls. The odds of cases being HIV positive were 10.83 times that of controls (OR=10.83, 95%CI: 3.19-36.78, p<0.01).

***Conclusion*: This study found that the socioeconomic status, including formal education level attained, prior screening, and HIV sero-positivity were associated with development of cervical cancer in Rwanda. Cervical cancer education and screening programs should consider these factors and serve the high-risk population.**

INTRODUCTION

Cervical cancer is the fourth most common cancer in women worldwide and the second in low- and middle-income countries (LMICs) (1). In 2018, an estimated 569,800 new cervical cancer cases and 311,400 deaths from cervical cancer were reported worldwide, accounting for 7.5% of all women cancer deaths worldwide (1). Approximately, the majority (85%) of cervical cancer related mortality occurs in LMICs, and this is expected to increase up to 98% by 2030 (1,2). The cervical cancer incidence rate in East Africa is the highest in the world, with 40.1 new cases per 100,000 women per year compared to incidence rate of 4 to 10 in most of the high income countries (3). Apart from the direct costs to patients, the economic cost due to loss of workforce productivity is high, as most affected women are still in productive age groups (4).

Despite being among the leading causes of cancer deaths in women worldwide, cervical cancer is preventable and curable when detected and treated early (5). Many risk factors have been found to contribute to the development of cervical cancer (6), and knowing those factors can assist in early diagnosis and treatment (7). Identifying the risk factors for cervical cancer in a specific community informs the design of prevention programs adapted to the local context.

In Rwanda, cervical cancer is the most frequently diagnosed cancer among women, with estimates of nearly 1,304 newly diagnosed cases and 921 associated deaths per year (8). Cervical cancer natural history consists in progression from precancerous lesions to invasive cervical cancer which also progresses from stage I through stage IV; the higher the stage, the poorer the prognosis (9). Rwanda has, since 2011, achieved more than 90% young girls HPV vaccine coverage (10). However, an effective screening program is still needed for cervical cancer prevention and early detection(11). In Rwanda, no available data about cervical cancer screening coverage but it is suspected to be low, as in other low-income countries. As a consequence, about 97% of cervical cancer cases are being diagnosed at late stages (2)(8)(12). This study hypothesized the risk factors of cervical cancer in Rwanda are different from those established in developed countries. The identification of these factors will inform the establishment of proper policies for cervical cancer prevention program adapted to local settings. Yet, there are no available data about the characteristics of women who develop cervical cancer in Rwanda. Accordingly, this study was conducted to address this gap in knowledge.

MATERIALS AND METHODS

Settings

This study was conducted at the University Teaching Hospital of Kigali, Rwanda. An average of 20-30 patients a week was seen in

the Gynecologic Oncology Clinic where majority of cervical cancer patients were referred from all over the country for the only countrywide available Gynecology oncologist evaluation.

Design, sample size and sampling

This study utilized a case control study design relying on the review of files of patients who attended the gynecologic oncology clinic between January 2014 and December 2018. The target study population was all women who were diagnosed with cervical cancer at the clinic.

Files of patients who attended the Gyn-oncology clinic from January 2014 to December 2018 were reviewed and categorized into cases and controls. Patients with histopathology-confirmed cervical cancer (cases) were matched with patients with no cervical cancer diagnosis (controls) by age (± 1 year); with the ratio of one to two. The estimated sample size was 189, based on a formula for case control studies (13), with 90% power, 5% type I error, and 1 case to 2 control ratio.

Data collection

A data collection form was created to extract information from patients' files. All files of patients who attended the Gyn-oncology clinic during the study period were reviewed, all cases were extracted. The rest of the files were randomly selected to identify controls until the desired sample size was achieved. No patient identifiers were collected except the file number for the purpose of counter-checking information. Once data were cleaned, all file numbers were removed from the data set.

Ethical considerations

This study was approved by the Institutional Review Board of the University of Global Health Equity (UGHE-IRB protocol 0055) and by the Research Ethics Committee of the University Teaching Hospital of Kigali (ref. EC/CHUK/745/2018). Furthermore, patient identity was not revealed at any stage of the study.

Variables

Variables collected included age, number of full-term deliveries, history of oral contraceptive pills use, history of smoking, age at first sexual intercourse, age at first pregnancy, HIV status, number of sex partners, history of previous cervical cancer screening, and history of sexually transmitted diseases.

Data management

All data extracted from patient files were entered to MS Excel for cleaning. The dataset was then uploaded to SPSS version 20 for analysis. Descriptive statistics were used to summarize the characteristics of patients. Fisher's Exact test was used to test the association between patients' characteristics and diagnosis of cervical cancer. Pairwise deletion was done for variables with missing data. Variables with $p < 0.20$ were further analyzed by using backward stepwise logistic regression, with P-value set at 0.05.

RESULTS

Information from 243 patient files was included in the study, with 81 (33.3%) cases matched with 162 (66.7%) controls by age (± 1 year). There were no significant differences between the two samples in mean age (p=0.85) and in age groups (p=0.94) (Table 1).

Table 1

Age distribution of case and control samples

		Control	Case	P-value
Sample	**(n=243)**	**162 (66.7%)**	**81 (33.3%)**	
Age	Mean (±SD)	50.8 (±9.4)	51.1 (±9.5)	0.85
	≤35	9 (5.6%)	3 (3.7%)	0.94
	>35 and ≤ 50	70 (43.2%)	34 (42%)	
	>50 and ≤ 65	74 (45.7%)	40 (49.4%)	
	>65	9 (5.6%)	4 (4.9%)	

Seven variables were found significantly associated with the diagnosis of cervical cancer, they were: 1) level of education ($p<0.01$), 2) socioeconomic class ($p<0.01$), 3) marital status ($p<0.01$), 4) the number of full-term deliveries ($p=0.02$), 5) HIV status ($p<0.01$), 6) age at first sexual intercourse ($p<0.01$),7) age at first pregnancy ($p<0.01$) (Table 2). No significant association was found between cervical cancer and smoking history ($p=0.24$), history of sexually transmitted diseases ($p=0.487$), history of oral contraceptive pill use ($p=0.35$), number of sexual partners ($p=0.05$); and prior cervical cancer screening ($p=0.54$) (Table 2).

Table 2

Variables associated with cervical cancer in bivariate analysis

Patients' characteristics		**Controls N (%)**	**Cases N (%)**	**P-value**
Sample		**162**	**81**	**NA**
Education level	No education	23 (14.2%)	28 (34.6%)	<0.01*
	Primary education	65 (40.1%)	42 (51.9%)	
	Secondary education	48 (29.6%)	9 (11.1%)	
	Bachelor level	26 (16.0%)	2 (2.5%)	
Socio-economic class	Low	52 (32.1%)	56 (69.1%)	<0.01*
	Moderate	102 (63.0%)	25 (30.9%)	
	High	8 (4.9%)	0 (0.0%)	
Marital status	Never married	1 (0.6%)	3 (3.7%)	<0.01*
	Married	116 (72.0%)	46 (56.8%)	
	Widowed	28 (17.4%)	28 (34.6%)	
	Divorced	16 (9.9%)	4 (4.9%)	
Smoking history	Never smoked	137 (87.8%)	65 (80.2%)	0.24
	Smoked unknown duration	18 (11.5%)	15 (18.5%)	
	Smoked 1-5 years	1 (0.6%)	1 (1.2%)	
Number of deliveries	0	2 (1.2%)	1 (1.2%)	0.02*
	1-3	51 (31.7%)	12 (15.0%)	
	4-6	68 (42.2%)	33 (41.2%)	
	7-9	30 (18.6%)	27 (33.8%)	
	10 or more	10 (6.2%)	7 (8.8%)	
Number of sexual partners	>1 partner	57 (40.7%)	44 (55.0%)	0.05
	1 partner	83 (59.3%)	36 (45%)	
HIV status	Unknown	25 (15.5%)	18 (22.2%)	<0.01*
	Negative	123 (76.4%)	46 (56.8%)	
	Positive	13 (8.1%)	17 (21.0%)	
History of STDs	No	131 (81.9%)	60 (77.9%)	0.49
	Yes	29 (18.1%)	17 (22.1%)	
History of OCPs use	Never used	134 (83.8%)	73 (90.1%)	0.35
	Less than 5 years	24 (15.0%)	8 (9.9%)	
	5 to 10 years	2 (1.2%)	0 (0.0%)	
Prior cervical cancer screening	Never screened	154 (95.7%)	76 (93.8%)	0.54
	Yes	7 (4.3%)	5 (6.2%)	
Age at first sex	≤16	37 (22.8%)	9 (11.1%)	<0.01*
	>16 and ≤21	74 (45.7%)	55 (67.9%)	
	>21	51 (31.5%)	17 (21.0%)	
Age at first pregnancy	≤ 16	23 (14.2%)	8 (9.9%)	0.01*
	17 and ≤21	61 (37.7%)	45 (55.6%)	
	22 and less than 25	45 (27.8%)	24 (29.6%)	
	25 or above	33 (20.4%)	4 (4.9%)	

** Statistically significant at P=0.05*

In multivariate analysis, five variables were found to be significantly associated with cervical cancer: education level, socioeconomic class, marital status, number of deliveries and HIV status were found to be significantly associated with cervical cancer diagnosis. The odds of cases having a secondary education were 0.15 times (OR=0.15, 95%CI: 0.04-0.058, p<0.01) the odds of controls. The odds of cases being in moderate socioeconomic class were 0.37 times (OR=0.37, 95%CI: 0.17-0.82, p=0.01) the odds of controls. The odds of cases were 14.1 times the odds of controls to be never married (but sexually active) patients (OR=14.10, 95%CI: 1.07-185.49, p=0.04) and 2.45 times the odds of controls to be widowed (OR=2.45, 95%CI: 1.05-5.71, p=0.04) compared to married patients. The odds of cases having 1 to 3 previous deliveries were 0.1 times the odds of controls (OR=0.1, 95%CI: 0.02-0.48, p<0.01). The odds of cases to be HIV positive were 10.83 times the odds of controls (OR=10.83, 95%CI: 3.19-36.78, p<0.01) (Table 3).

Table 3

Results of multivariate analysis

Patients' characteristics		**p-value**	**OR**	**95% CI**
Education level	No education	Ref		
	Primary education	0.51	0.75	0.32-1.77
	Secondary education	<0.01	0.15	0.04-0.58*
	Bachelor level	0.24	0.28	0.03-2.38
Socioeconomic class	Low	Ref		
	Moderate	0.01	0.37	0.17-0.82*
	High	0.10	<0.001	<0.01- NA
Marital status	Married	Ref		
	Never married	0.04	14.10	1.07-185.49*
	Widowed	0.04	2.45	1.05-5.71*
	Divorced	0.48	0.59	0.13-2.57
Number of deliveries	0 deliveries	Ref		
	1-3 deliveries	<0.01	0.1	0.02-0.48*
	4-6 deliveries	0.29	0.49	0.13-1.85
	7- 9 deliveries	0.44	0.61	0.17-2.15
	10 or more deliveries	0.41	0.51	0.1-2.58
Number of sex partners	1 partner	Ref		
	More than 1 partner	0.07	0.51	0.24-1.07
HIV status	Negative	Ref		
	Positive	<0.01	10.83	3.19-36.78*
Age at first pregnancy	<= 16	Ref		
	>16 < =21	0.28	1.90	0.60-6.07
	>=21 < 25	0.07	3.25	0.90-11.69
	>25	0.32	0.44	0.09-2.22

DISCUSSION

The WHO recommends that women between the ages of 30 and 49 years should be screened for cervical cancer since they are in a higher risk age range (14). In this study, the majority of cervical cancer patients were diagnosed around this age range. A similar finding was reported in another study in Nigeria (15). The results suggested that screening programs targeting the age range recommended by WHO could potentially contribute to the reduction of the burden of cervical cancer in Rwanda.

Similar to several previous studies, patients' education level, socioeconomic class, marital status, number of deliveries and HIV status were found to be associated with cervical cancer diagnosis. Education level and socioeconomic class have been consistently found to be inversely associated with cervical cancer risk (16). Most people with lower level of education and socioeconomic class in many developing countries, including Rwanda, do not attend cervical cancer screening, which in turn leads to higher rates of diagnosis of cervical cancer at late stages (2). Some other known factors associated with higher cervical cancer risk including early age at first sexual intercourse, early age at first pregnancy and high parity are also associated with low socioeconomic status (6).

Marital status was found to be significantly associated with cervical cancer diagnosis. Compared to married patients, never married and widowed patients were more likely to be diagnosed with cervical cancer. Other previous studies showed similar results with the assumption that married people are more likely to be in stable relationships and have fewer sexual partners; having multiple sexual partners is a known risk factor of cervical cancer (17). The study finding showed a nearly significant association between the number of sexual partners and cervical cancer. However, since the study data were extracted from routine medical records, the answers about having multiple sex partners could have been affected by the way the question was asked, whether it was asked as in lifetime or over a specified time, or by the patients not being honest in disclosing their sensitive sexual life information.

Previous research studies found an association between cervical cancer diagnosis and number of deliveries (6,18). The risk of cervical cancer increased with increasing number of full-term deliveries in HPV positive women (19). The finding of this study was slightly different - women with one to three deliveries were less likely (OR=0.1) to be diagnosed with cervical cancer compared to those who never delivered. However, in this study sample, the number of women with 0 delivery was very small, study with larger sample size should be conducted in the future to investigate its true effect.

Similar to the finding of this study, many studies have found significantly higher risk of cervical cancer among HIV positive patients, especially in LMICs (10). One study conducted in Rwanda in 2016 found higher HPV prevalence and increasing cervical cytology severity among HIV positive women (10). HPV infection is an underlying cause of cervical cancer (7). HIV infection compromises the immunity and leads to persistent HPV infection, which eventually can progress to precancerous lesions and invasive cervical cancer (20). This high risk of progression to cancer means that cervical cancer screening and prevention services should be an integral part of HIV treatment programs.

Cervical cancer screening is a proven intervention to reduce cervical cancer

incidence in developed countries (21). In this study, the majority (94.6%) of patients in both case and control groups did not have cervical cancer screening prior to the consultation, as cervical cancer screening programs in Rwanda as well as in many developing countries were lacking (2). Policy makers and program managers should consider establishing more nationwide screening programs in order to reduce cervical cancer morbidity and mortality.

Study limitations

Since this study relied on analyzing routine clinical data from hospital patient records, some limitations related to missing and inaccurate data were inevitable. Moreover, the study was conducted at a public referral hospital; the results do not necessarily represent the general Rwandan cervical cancer patient population, especially with respect to socioeconomic status.

CONCLUSION

This study found that the risk factors of cervical cancer in Rwanda are similar to those reported in other studies. Education level, socioeconomic class, marital status, number of deliveries, and HIV status were found to be significantly associated with cervical cancer development. Cervical cancer education and screening programs should consider these factors and serve the high-risk population.

REFERENCES

1. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Znaor A, Mathers C, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer. 2019;144(8):1941–53.

2. Bradford L, Goodman A. Cervical cancer screening and prevention in low-resource settings. Clin Obs Gynecol [Internet]. 2013;56(1):76–87. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23337844

3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin [Internet]. 2018;68(6):394–424. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30207593

4. Dubas-Jakóbczyk K, Kocot E, Seweryn M, Koperny M. Production lost due to cervical cancer in Poland in 2012. Med Pr [Internet]. 2016;67(3):289–99. Available from: http://www.journalssystem.com/medpr/Production-lost-due-to-cervical-cancer-in-Poland-in-2012,61068,0,2.html

5. Ghebreyesus AT, WHO. Cervical cancer: an NCD We Can Overcome. In Geneva, Switzerland: World Health Organization; 2018 [cited 2018 Aug 1]. Available from: http://www.who.int/reproductivehealth/DG_Call-to-Action.pdf

6. Momenimovahed Z, Salehiniya H. Incidence, mortality and risk factors of cervical cancer in the world. Biomed Res Ther [Internet]. 2017;4(12):1795. Available from: http://www.bmrat.org/index.php/BMRAT/article/view/386

7. Walboomers JMM, Jacobs M V., Manos MM, Bosch FX, Kummer JA, Shah K V., et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999;189(1):12–9.

8. Bruni L, Albero G, Serrano B, Mena M, Gómez D, Muñoz J, et al. Human Papillomavirus and Related Diseases Report [Internet]. ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre). 2019. Available from: https://hpvcentre.net/statistics/reports/XWX.pdf

9. Myers ER, McCrory DC, Nanda K, Bastian L, Matchar DB. Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis. Am J Epidemiol. 2000;151(12):1158–71.

10. Ngabo F, Franceschi S, Baussano I, Umulisa MC, Snijders PJF, Uyterlinde AM, et al. Human papillomavirus infection in Rwanda at the moment of implementation of a national HPV

vaccination programme. BMC Infect Dis [Internet]. 2016;16(1):1–10. Available from: http://dx.doi.org/10.1186/s12879-016-1539-6

11. Ouh YT, Lee JK. Proposal for cervical cancer screening in the era of HPV vaccination. Obstet Gynecol Sci. 2018;61(3):298–308.

12. Davey S, Mpanumusingo E, Fehr A, Butonzi J, Shyirambere C, Hategekimana V, et al. Characteristics and early outcomes of cervical cancer patients at Butaro District Hospital, Rwanda: a retrospective review. Lancet Glob Heal [Internet]. 2017;5:S28. Available from: http://linkinghub.elsevier.com/retrieve/pii/S2214109X17301353

13. Charan J, Biswas T. How to calculate sample size for different study designs in medical research? Indian J Psychol Med [Internet]. 2013;35(2):121–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24049221%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC3775042

14. WHO. WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention [Internet]. 2013. Available from: https://apps.who.int/iris/bitstream/handle/10665/94830/9789241548694_eng.pdf?sequence=1

15. Musa J, Nankat J, Achenbach CJ, Shambe IH, Taiwo BO, Mandong B, et al. Cervical cancer survival in a resource-limited setting-North Central Nigeria. Infect Agent Cancer [Internet]. 2016;11(1):1–7. Available from: http://dx.doi.org/10.1186/s13027-016-0062-0

16. Parikh S, Brennan P, Boffetta P. Meta-analysis of social inequality and the risk of cervical cancer. Int J Cancer. 2003;105(5):687–91.

17. Liu Z-C, Liu W-D, Liu Y-H, Ye X-H, Chen S-D. Multiple Sexual Partners as a Potential Independent Risk Factor for Cervical Cancer: a Meta-analysis of Epidemiological Studies. Asian Pac J Cancer Prev [Internet]. 2015;16(9):3893–900. Available from: http://journal.waocp.org/article_31004_b1170e88ea14caa9963f6b9599324409.pdf

18. International Collaboration of Epidemiological Studies on Cervical cancer. Cervical carcinoma and reproductive factors: Collaborative reanalysis of individual data on 16,563 women with cervical carcinoma and 33,542 women without cervical carcinoma from 25 epidemiological studies. Int J Cancer. 2006;119(5):1108–24.

19. Muñoz N, Franceschi S, Bosetti C, Moreno V, Herrero R, Smith JS, et al. Role of parity and human papillomavirus in cervical cancer: the IARC multicentric case-control study. Lancet [Internet]. 2002;359(9312):1093–101. Available from: http://www.sciencedirect.com/science/article/pii/S0140673602081515%0Ahttp://www.journals.cambridge.org/abstract_S1041610212000816

20. Ferenczy A, Coutlée F, Franco E, Hankins C. Human papillomavirus and HIV coinfection and the risk of neoplasias of the lower genital tract: a review of recent developments. CMAJ. 2003;169(5):431–4.

21. WHO. Cervical cancer screening in developing countries: Report of a WHO consultation [Internet]. WHO. Geneva; 2002. Available from: https://apps.who.int/iris/bitstream/handle/10665/42544/9241545720.pdf;jsessionid=2F02AEB3C9F0E7280FF198C98C21248F?sequence=1