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ORIGINAL ARTICLE

Reproductive and Lifestyle Characteristics in Kenyan Women Presenting With Precancerous Cervical Lesions

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ABSTRACT

Background: Cervical cancer is a leading cause of cancer in women, accounting for 68% of cancer-related deaths among women in developing countries. Several reproductive, lifestyle and demographic risk factors are associated with increased risk for cervical cancer. This study examined the association of risk factors with precancerous cervical lesion grade in women attending Nakuru County Referral Hospital.

Methods: This hospital-based, case-control study was conducted among women aged 20 to 70 years from January to December, 2017. A total of 142 women were recruited into the study and stratified based on precancerous cervical lesion grades based on the Bethesda System as: atypical glandular cells or adenocarcinoma in situ (AGC/AIS, n=8), high squamous intraepithelial lesions (HSIL, n=59), low squamous intraepithelial lesions (LSIL, n=35), and controls (n=40). Structured questionnaires were used to collect information on demographic, reproductive health, and lifestyle characteristics; anthropometric assessments were conducted. Endocervical swabs and scrapings were obtained from the study participants and used for HPV-16/18, and Pap smear screening.

Results: Age differed significantly among the study groups, with age rising with higher grade of precancerous lesion. Higher rates of HPV-16/18 infection was associated with presenting with AGC/AIS (n=8, 100.0%), HSIL (n=47, 79.7%), and (n= 29, 82.9%), compared to controls (n=4, 10.0%; P<0.0001). History of concomitant lower abdominal pain, vaginal bleeding and discharge was associated with higher risk of precancerous lesion in the HSIL group (adjusted odds ratio [AOR] 8.9; 95% Confidence Interval [CI], 2.6 to 30.6) and the LSIL group (AOR 5.8; 95% CI, 1.8 to 18.8). Bust circumference <99 cm was associated with higher risk of having AGC/AIS (AOR 17.4; 95% CI, 1.1 to 276.0), HSIL (AOR 5.9; 95% CI, 2.0 to 17.1), and LSIL (AOR 2.7; 95% CI, 0.9 to 7.8). Waist circumference < 86 cm was associated with higher risk of HSIL (AOR, 5.4; 95% CI, 1.9 to 15.4) and LSIL (AOR 2.9; 95% CI, 0.9 to 8.2). Having a healthy diet was associated with higher odds of LSIL (AOR, 4.2; 95% CI, 1.4 to 12.9), but was not associated with HSIL or AGC/AIS.

Conclusion: This study suggests that HR HPV-16/18 infection, chronic lower abdominal pain with vaginal bleeding, and decreased upper and lower trunk body mass, are associated with higher risk of precancerous cervical lesions. Integrating targeted cervical cancer screening in routine reproductive health care services may reduce the risk of developing cervical cancer.

INTRODUCTION

Globally, cervical cancer is the fourth most common cancer in women, with an estimated 570,000 new cases and 311,000 deaths in 2018. The burden of cervical cancer is particularly high in sub-Saharan Africa, where it ranks among the top two most commonly diagnosed cancers in women, and is a leading cause of cancer-related deaths.[1],[2] [3]. In Kenya, over 2000 cervical cancer cases are diagnosed per 100,000 women annually, resulting in an estimated 8,600 deaths in the country each year.[4]

Cervical intraepithelial lesions are the precancerous condition of the cervix, which if left untreated, can develop to cervical cancer. These lesions are characterized by abnormal cellular morphology and are detectable by microscopic examination of cervical epithelial cells obtained through Pap smears. The Bethesda system (TBS) is used to grade the severity of abnormal cell morphology. The most common manifestation of precancerous cervical lesions are low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL) both of which both are treatable by cervical ablation, cryotherapy or loop electro-excision procedure (LEEP).[11],[16] If left untreated, lesions may prog-

ress, and infiltrate adjacent tissue, at which point the disease is diagnosed as an invasive squamous cell carcinoma or, more rarely, a glandular cell cervical cancer (adenocarcinoma).[17] At this stage, management of lesions is more difficult, and a total abdominal hysterectomy may be recommended in tandem with radiotherapy and/or chemotherapy treatments if metastasis has occurred.[17]

A number of reproductive, lifestyle and demographic risk factors are associated with increased risk for development of cervical cancer. HIV-induced immunodeficiency predisposes women to develop precancerous cervical lesions by enhancing gene expression of oncogenic human papillomavirus (HPV) strains such as high risk (HR) HPV- I6/18,[5] with immunosuppression increasing risk of progression to cancer. [6]-[9] Like HIV, HPV is sexually transmitted, and risk of cervical cancer is associated with sexual risk factors including multiplicity of sexual partners, early sexual debut, high parity and long-term use of hormonal birth control <refs>. Demographic factors that have been associated with increased risk of cervical cancer include alcohol and tobacco use, low education, and low socioeconomic status <refs needed>. Malnutrition and wasting, may also contribute to increased risk of development of precancerous cervical lesions in individuals with HPV infection. <authors to add statement to describe how> <good refs are needed>

To address the high burden of cervical cancer in the country, in June 2019 the Kenyan government implemented mass immunization of adolescent girls with the HPV vaccine to prevent HPV infections prior to the onset of sexual debut<reference needed>. However, many Kenyan women are already infected with HPV, and remain at risk for development of cervical cancer. In the absence of routine screening for cervical intraepithelial lesions though Pap smear, these women may have precancerous cervical lesions that could progress over time. In order to identify subsets of women at greatest risk of cervical cancer, this study examined the association of reproductive health and lifestyle practices with precancerous cervical lesion grades in women attending Nakuru County Referral Hospital (NCRH).

METHODS

Study Site

The study was conducted at the Reproductive Health Services Department of the Maternal and Child Health (MCH) Unit at NRCH, a 250-bed capacity referral hospital in Nakuru County, Kenya serving a population of about 1.2 million residing in the city of Nakuru, its suburbs and rural environs.[20] The MCH Unit provides medical services for maternal health, including reproductive health, birth control and pre and post natal services. Monthly outpatient attendance at the MCH unit ranges from 150 to 200 women.

Study Design and Selection of Study Participants

This hospital-based, case-control study assessed the relationship of reproductive and lifestyle factors with precancerous cervical lesion grades in women attending outpatient reproductive health services at the MCH Unit of NRCH from January to December of 2017. Four groups of women were recruited into the study, based on findings from cervical visual inspection with acetic acid and lugol's iodine (VIA/VILI test) . The groups were: 1) women with atypical glandular cells or adenocarcinoma in situ (AGC/AIS, n=8), 2) women with high squamous intraepithelial lesions (HSIL, n=59), 2) women with low squamous intraepithelial lesions (LSIL, n=35), and 4) control women in whom no abnormal cellular morphology was observed.<Author to describe how participants were recruited in 4 study groups> All women seeking reproductive health services from the MCH on clinic visit days where screened for eligibility and exclusion criteria. Eligibility criteria were:<authors to complete> . Eligibility criteria were:<authors to complete> .

Sampling Procedure and Sample Size

We calculated the minimum sample size needed to estimate the odds ratio (OR) for having a precancerous lesion associated with explanatory factors using the following formula[21]:

Here, $Z\alpha$ is the value 1.96 for a 95% confidence interval (CI), $Z\beta$ is the value 0.84 for 80% power, $\pi 1$ is the proportion of controls with the exposure, $\pi 2$ is an auxiliary variable equal to OR x $\pi 1/(1-\pi 1+\text{OR x } \pi 1)$, πo is $(\pi 1+\pi 2)/2$, m is the number of controls per case, and n is the required sample size per case and control group. We applied this formula assuming pairwise comparisons between controls and each category of precancerous lesions, and that the ratio between controls and cases would be approximately 1. Our minimum OR of interest was 3.5, and we assumed that explanatory factors would be present in 25% to 75% of the control group. Using this formula we obtained a minimum sample size of about 40 per group. The study included a total of 142 participants, including 40 controls, 35 women in the LSIL group, 59 women in the HSIL group and 8 women in the AGC/AIS group.

Data Collection and Laboratory Investigations

Data collection procedures were conducted by clinical staff, including nurses, pathologists and cytotechnicians from Nakuru County Referral Hospital; all study staff underwent a structured protocol training prior to study commencement. Information on participant demographics, reproductive health and lifestyle practices, diet and physical exercise were captured in one-on-one interviews conducted in the XX language with study participants using a structured questionnaire. If a participant did not understand a question, or provided an ambiguous response, the interviewer probed for greater depth or clarity using structured questionnaire probes, which were designed based on validated probes from similarly designed studies.[9],[22],[23]. Information on diet was obtained through questions regarding weekly food intake using a checklist of food items common in Nakuru

TABLE 1. Characteristics of the Study Participants (N=142)

Characteristic	Controls, n=40 n (%)	LSIL, n=35 n (%)	HSIL, n=59 n (%)	AGC/AISa, n=8 n (%)	*P* value
Median age, years[a]	34 (21-55)	38 (20-57)	42 (27-63)	65 (50-70)	<0.001
Education					
≤Primary	21 (52.5)	17 (48.6)	43 (72.9)	5 (62.5)	
>Secondary	19 (47.5)	18 (51.4)	16 (27.1)	3 (37.5)	0.017
Occupation					
Informal sector	21 (52.5)	15 (42.9)	33 (55.9)	6 (75)	
Small businesses	15 (37.5)	15 (42.9)	19 (32.2)	2 (25)	
Formal employment	4 (10)	5 (14.3)	7 (11.9)	0 (0)	0.879
Marital status					
Married	30 (75)	21 (60)	35 (59.3)	3 (37.5)	
Single	10 (25)	14 (40)	24 (40.7)	5 (62.5)	0.401
HR HPV16/18					
Yes	4 (10)	29 (82.9)	47 (79.7)	8 (100)	
No					<0.001
History of lower abdominal pain, vaginal bleeding or discharge					
Yes	30 (75)	33 (94.3)	56 (94.9)	8 (100)	
No	10 (25)	2 (5.7)	3 (5.1)	0 (0)	0.008
Birth control use					
Hormonal	18 (45)	18 (51.4)	33 (56)	0 (0)	
Non-hormonal	16 (40)	10 (28.6)	14 (23.7)	0 (0)	
None	6 (15)	7 (20)	12 (20.3)	8 (100)	0.001
Parity					
≥2	22 (55)	19 (54.3)	37 (62.7)	7 (87.5)	
<2	18 (45)	16 (45.7)	22 (37.3)	1 (12.5)	0.001
Number of sexual partners					
>1	10 (25)	13 (37.1)	30 (50.8)	2 (25)	
≤1	30 (75)	22 (62.9)	29 (49.2)	6 (75)	0.079

[a]Median and range

TABLE 2. Multivariate Logistic Regression Analysis of Reproductive Risk Factors and Cervical Lesion Group

Characteristic	Adjusted Odds Ratio[a]	95% CI	*P* value
HR HPV 16/18			
Control	Ref		
LSIL	50.1	11.9-208.9	<0.001
HSIL	36.3	9.5-139.5	<0.001
AGC/AIS	1.9	1.9-1.9	<0.001
History of lower abdominal pain and vaginal bleeding			
Control	Ref		
LSIL	5.8	1.8-18.7	0.003
HSIL	8.9	2.6-30.6	0.001
AGC/AIS	1.0	1.0-1.0	<0.001
Parity ≥2			
Control	Ref		
LSIL	0.8	0.3-2.4	0.699
HSIL	0.5	0.18.-1.5	0.231
AGC/AIS	1.6	0.0-74.5	0.813
Sex partners >1			
Ref			
LSIL	1.1	0.3-5.0	0.755
HSIL	3.9	0.9-16.5	0.068
AGC/AIS	0.5	0.0-23.9	0.216

[a]Each explanatory factor was regressed against cervical lesion category, adjusting for age, birth control method, cervical cancer disease awareness, marital status and education

County. Study participants were also asked questions regarding the type, frequency and intensity of their physical activity on weekly basis. Questions on diet and physical activity were developed based on published methodologies of studies collecting similar data.[24],[25] <Authors must describe and justify categories of healthy versus unhealthy diet, which they used in tables>Study participants underwent anthropometric assessment including measurement of body weight, height, mean-upper-arm circumference (MUAC), bust girth and waist circumference. Data on body weight in kilograms and height in meters were used to calculate the body mass index (BMI).

Cervical wall specimens were collected on all study participants for assessment of abnormal cellular morphology and detection of HR HPV-16/18. Briefly, scrapes were excavated from the cervical wall using a cervical brush; scraped tissue embedded in the brush was smeared onto microscopic glass slides, fixed while wet, stained after drying using Papanicalou staining techniques and dyes (Heamatoxylin, EA 50 and OG 6) and mounted.[27] Smears were microscopically examined for the presence of abnormal cellular morphology and graded using TBS.[18],[28] Study participants were categorized into four discrete cytology categories based on their TBS score as: control (ie, no cytological abnormality), LSIL, HSIL and AGC/AIS. All smears positive for cervical cancer (ie, AGC/AIS) were confirmed by an independent clinical cytologist. All cervical specimens underwent assessment for HR HPV-16/18 using a commercial kit (StrongStep® HPV 16/18 Antigen Rapid Test Device,Limingo Bio), that detects viral antigens.[26]

Data Analysis

Study questionnaires were data entered into into Microsoft Office Excel software and then exported into IBM SPSS Statistics for Windows version 21.0 (IBM Corp, Armonk, NY, USA), where data were checked for presence of outliers and data errors. Bivariate analyses were conducted to assess associations between reproductive health and lifestyle factors and cervical cytology category. In bivariate analyses, Kruskal-Wallis and ANOVA tests were used to test for differences in continuous variables across cytology category; chi-square and Fishers exact tests were used to test for differences across categorical variables. Multivariable logistic regression was conducted to estimate odds ratios (OR) for abnormal cytology associated with explanatory factors; with the control group treated as the reference category. One model was developed for each explanatory factor, where the explanatory factor was regressed against cervical lesion category; age, birth control method, cervical cancer disease awareness, marital status and education were included in each model as potential confounders. <I recommend removing the Dunn's post-hoc analysis from the manuscript, or provide a clear explanation of what it is in the methods and how results should be interpreted>

Ethical Considerations

Written informed consent was conducted in all study participants prior to carrying out any study procedures. Regardless of their willingness to consent, women with abnormal cytology results were counseled and advised to seek further clinical management from the health care providers in the MHC clinic. Ethical approvals were obtained from Kenyatta University Ethical Research Committee (KUERC-KU/R/COMM/51/228; PKU/141/I124) and the Kenya National Council of Science Technology and Innovation (NACOSTI-NACOSTI/RC-D/12A/013/148). Institutional approval was provided by the Nakuru County Referral Hospital (RII/VOL.I/08). <Authors to state if data were anonymised>

RESULTS

In total, 142 women were enrolled in the study, with a mean age of ## years. Most women were married (%), had not com-

TABLE 3. Anthropometric, Diet and Physical Activity Characteristics of the Study Participants

Characteristic	Controls, n=40 n (%)	LSIL, n=35 n (%)	HSIL, n=59 n (%)	AGC/AIS[a], n=8 n (%)	*P* value n (%)
Weight[a], kg	71 (45-89)	70 (45-70)	70 (44-96)	73 (52-86)	0.035
Height[a], m	1.6 (1.5-1.8)	1.6 (1.5-1.8)	1.6 (1.5-1.8)	1.6 (1.5-1.6)	0.763
BMI[a], kg/m²	26 (19-34.0)	25 (20-35)	24 (16-33)	27.5 (21-33)	0.570
MUAC[a], cm	33 (23-45)	31 (20-44)	30 (21-42)	32 (23-34)	0.110
Bust[a], cm	103 (78-122)	100 (70-122)	98 (74-126)	96 (76-101)	0.004
Waist[a], cm	90 (51-109)	86 (54-114)	83 (56-112)	74 (64-90)	0.005
Physical activity					
Yes	22 (80.0)	33 (94.3)	56 (94.9)	8 (100)	
No	8 (20.0)	2 (5.7)	3 (5.1)	0 (0)	0.050
Diet					
Healthy	13 (33.0)	11 (31.4)	39 (66)	5 (62.5)	
Unhealthy	27 (70.0)	24 (68.6)	20 (34)	3 (37.5)	0.004
Ever use alcohol					
Yes	3 (7.5)	3 (8.6)	6 (10.2)	1 (12.5)	
No	37 (92.5)	32 (91.4)	53 (89.8)	7 (87.5)	0.825
Ever use tobacco					
Yes	1 (2.5)	2 (5.7)	6 (10.2)	1 (12.5)	
No	39 (97.5)	33 (94.3)	53 (89.8)	7 (87.5)	0.328

[a]Median (range)

pleted secondary education (%), and were employed in the informal sector (%). Several demographic variables were associated with detection of abnormal cytology in bivariate analysis. Women presenting with AGC/AIS had a significantly higher median age in years (65; range, 50 to 70 years) years compared to women with HSIL (42; range, 27 to 63 years)), LSIL (38; range, 20 to 57 years years), and controls (34; range, 21 to 55 years; *P* value<.001) (Table 1). The proportion of the women with less than a secondary education was higher in the AGC/AIS (n=5, 62.5%) and HSIL groups (n=43, 72.9%) compared to the LSIL (n=17, 48.6%) and control groups (n=21, 52.5%; *P* value=0.079). The distribution of occupational types and marital status were similar across cervical cytology groups.

In bivariate analysis, several reproductive risk factors were more frequent in women with abnormal cervical cytology compared to controls, with frequency increasing with higher category of abnormality. History of lower abdominal pain with vaginal bleeding was significantly higher in the AGC/AIS (n=8, 100.0%), HSIL (n=54, 91.5%), and LSIL groups (n=30, 85.7%) compared to controls (n=20, 50.0%; *P* value<.001). All women in the AGC/AIS group (n=8, 100.0%) reported not using any birth control methods, compared to a minority of women in the HSIL group (n=12, 20.3%), the LSIL group (n=7, 20.0%) and the control control (n=6, 15.0%; *P* value=.001). Parity ≥2 was higher among women in the AGC/AIS (n=7, 87.5%) and HSIL (n=37, 62.7%) groups compared to the LSIL (n=19, 54.3%) and control groups (n=22, 55.0%; *P* value=.001). Frequency of multiple sexual partners varied across cervical cytology group, though differences did not achieve statistical significance. Having multiple sexual partners was most common among women in the HSIL

TABLE 4. Multivariate Logistic Regression Analysis of Reproductive Risk Factors and Cervical Lesion Group

Characteristic	Adjusted Odds Ratio[a]	95% CI	*P* value
Body weight ≤68 kg			
Control	Ref		
LSIL	0.9	0.3-2.5	0.863
HSIL	2.2	0.8-5.9	0.103
AGC/AIS	0.2	0.0-5.8	0.317
Bust girth ≤ 99 cm			
Control			
LSIL	2.7	0.9-7.8	0.077
HSIL	5.9	2.0-17.1	0.001
AGC/AIS	17.4	1.1-276.1	0.043
Waist circumference ≤86 cm			
Control			
LSIL	2.9	0.9-8.2	0.051
HSIL	5.4	1.9-15.4	0.002
AGC/AIS	6.2	0.5-80.2	0.166
Has healthy diet			
Control			
LSIL	4.2	1.363-12.881	0.012
HSIL	1.1	0.391-3.062	0.864
AGC/AIS	0.0	0.000-4.065	0.177

[a]Each explanatory factor was regressed against cervical lesion category, adjusting for age, birth control method, cervical cancer disease awareness, marital status and education

(n=30, 50.8%) and LSIL groups (n=13, 37.1%), compared to women in the AGC/AIS (n=2, 25%) and control groups (n=10, 25.0%; *P* value=.079). Prevalence of HR HPV-16/18 was over 80% among women with abnormal cervical cytology, with the highest prevalence in the AGC/AIS group (n=8, 100.0%) compared to the HSIL group (n=47, 79.7%), the LSIL group (n=29, 82.9%) and the control group (n=4, 10.0%; *P* value<.001).

In bivariate analysis of anthropometric measurements, diet and activity revealed a number of differences across the cervical cytology groups. Median weight in kilograms was higher in the AGC/AIS group (73.0; range, 52.0 to 86.0 kilograms), compared to HSIL (70.0; range, 44.0 to 96.0 kilograms), LSIL (70.0; range, 45.0 to 70.0 kilograms) and controls groups (71.0; range, 45.0 to 89.0 kilograms; *P* value=.036) (Table 3). Median bust girth in centimeters (cm) was lower in the AGC/AIS (median, 96.0; range, 76.0 to 101.0 cm), HSIL (98.0; range, 74.0 to 126.0 cm), and LSIL (100.0; range, 70.0 to 122.0 cm) groups compared to the control group (73.0; range, 52.0 to 86.0 cm; *P* value=.004). Likewise, median waist circumference in centimeters was lower in women with AGC/AIS (74.0; range, 64.0 to 90.0 cm), HSIL (83.0; range, 56.0 to 112.0 cm), and LSIL (86.0; range, 54.0 to 114.0 cm) compared to controls (90.0; range, 51.0 to 109.0 cm; *P* value=0.002). Height, BMI and MUAC were similar across the cervical cytology groups. In all cervical cytology groups, 80% to 90% of women reported engaging in physical activity. The proportion of women with a healthy diet was was higher in the AGC/AIS (n=5, 62.5%) and HSIL (n=39, 66.0%) groups compared to the LSIL (n=11, 31.4%) and control (n=13, 33.0%; *P* value=.004) groups. The proportion of women reporting use of alcohol or tobacco use was low and did not vary significantly across the cervical cytology groups.

In logistic modelling, detection of HR HPV-16/18 was associated with a significantly higher risk of AGC/AIS (adjusted odds ratio [AOR] 1.9; 95% confidence interval [CI], 1.9 to X.X), HSIL (AOR 36.3; 95% CI, 9.5 to 139.5), or LSIL (AOR 50.1; 95% CI, 11.9 to 208.9) (Table 2). Likewise, a history of concomitant lower abdominal pain and vaginal bleeding was associated with higher risk of presenting with AGC/AIS (AOR 1.0; 95% CI, 1.0 to 1.0; P<.001), HSIL (AOR 8.8; 95% CI, 2.6 to 30.6), and LSIL (AOR 5.8; 95% CI, 1.8 to 18.7). Regression analyses also illustrated that high odds of having AGC/AIS (AOR 17.4; 95% CI, 1.1 to 276.0), HSIL (AOR 5.9; 95% CI, 2.0 to 17.1), and LSIL (OR 2.7; 95% CI, 0.9 to 7.8) were associated with a bust circumference ≤99 cm compared to a bust circumference > 99 cm (Table 4). In addition, waist circumference ≤ 86 cm was associated with a higher odds of HSIL (AOR, 5.4; 95% CI, 1.9 to 15.4) and LSIL (AOR 2.9; 95% CI, 0.9 to 8.2). Having a healthy diet was associated with higher odds of LSIL (AOR, 4.2; 95% CI, 1.4 to 12.9), but was not associated with HSIL or AGC/AIS.

Dunn's post hoc corrections were performed on significantly different Anova for, age, weight, bust and waist characteristics. Age results demonstrated that participants having AGC/AIS versus HSIL lesions were older relative to LSIL versus controls (P<0.01), Table 5: AGC/AIS versus HSIL**, AGC/AIS versus LSIL***, AGC/AIS versus Controls***, HSIL versusLSIL, HSIL versus Controls*** and LSIL versus Controls, P<0.05*; P<0.01**; P<0.001*** and not significant-(ns). Moreover, bust and waist girth for participants in HSIL study group versus control were reduced in comparison to LSIL versus control (P<0.01);HSIL versus control** (P<0.01).

DISCUSSION

This case control study, conducted at a large, public hospital in Kenya, examined the influence of demographic, reproductive and lifestyle factors on risk of precancerous cervical lesions, finding that older women with a low level of education had the highest prevalence of HR HPV 16/18 and were more likely to have the highest grade lesions. Consistent with the

sexual mode of HPV transmission, sexual and reproductive risk factors, including multiplicity of sexual partners, multiparity, and lack of birth control use were positively associated with abnormal cervical cytology. Strikingly, we detected HR HPV 16/18 in the cervical specimens of over 80% of women with abnormal cervical cytology, highlighting the importance of this viral strain as a cause of precancerous cervical lesions in Kenya.

Our finding that the median age of women was highest in the AGC/AIS group is consistent with other studies conducted in Africa and Europe, [6], [21], [22], [31], [32], [33], and likely reflects the progression of untreated, pre-cancerous cervical lesions over time. While over 90% of HPV infections clear within 2 years even without treatment, some infections, particularly those of oncogenic viral sub-types 16 and 18, may progress to cancer over a period of 10 to 20 years. Infection with HR HPV-16/18 strains was common among our study participants, which is consistent with the high prevalence of HR HPV -16/18 (>60%) in the general population in Kenya, and rates of detection of over 70% among patients at Kenyatta National Hospital diagnosed with high grade cervical lesions or squamous cell carcinomas [34]. Thus an accumulation of high grade lesions among older women may reflect the natural history of HPV 16/18 infection in a setting in which screening and treatment for precancerous cervical lesions is largely absent.

We found that over 90% of women with cervical lesions had concurrent lower abdominal pain, vaginal bleeding and vaginal discharge. In logistical analysis these signs and symptoms were associated with high risk for LSIL, HSIL and AGC/AIS grades, with risk increasing across higher category of cytological abnormality. These findings mirror those of studies conducted in the US and <authors to add> which found increased incidence of lower abdominal pain discomfort and vaginal bleeding among patients undergoing treatment for high grade precancerous cervical lesions.[36] <authors to add citations> The combination of abnormal vaginal bleeding and pelvic pain are common early indicators of metastasis of cervical cancer[37],[38]. However, these signs and symptoms were also reported 75% of our study controls, reflecting the low specificity of abdominal pain and vaginal bleeding as criteria for suspicion of precancerous cervical lesions. This lack of specificity underlies current recommendations to screen of all women at risk for cervical cancer, regardless of symptoms.

In our patient population, lack of birth control use and multiparity were significantly associated with detection of precancerous cervical lesions, which is consistent with other studies conducted in Nigeria, the U.S. and the U.K.[8],[39],[40],[41] Higher parity may increase the occurrence of ovarian hormone imbalances during and/or following pregnancy <ref needed>. These imbalances may perturb metaplastic processes during cervical wall development and differentiation in which columnar cells are converted to squamous cells within the transformation zone of parabasal layer of the cervical wall <ref needed>. Cells undergoing metaplasia are more vulnerable to HPV infection, due to numerous mitotic events which may concurrently propagate HPV DNA transcription in infected cells.[15]

Several studies from Africa, and the U.S. have reported increased risk of cervical cancer in association with having multiple sexual partners [22] [42] [43]. However, in logistic analysis controlling for demographic factors, we did not find an association between multiplicity of sexual partners and presence of precancerous cervical lesions. Higher transmission of HR HPV-16/18 strains is thought to underlie the association between multiple sexual partners and increased risk of precancerous cervical lesions or cervical cancer. However, in our study the much lower frequency of HR HPV-16/18 infection among control women was not coupled with a lower prevalence of having multiple sexual partners. We speculate that intervening factors, such as use of condoms, may be more frequent among controls women, though we did not collect data on this.

Against our expectation, our analysis revealed that having a healthy diet was more frequent among women in the HSIL and AGC/AIS groups compared to women in the LSIL and control groups. This contrasts with findings from a trial conducted in the U.S. suggesting that high consumption of cruciferous vegetables, which are common in the Kenyan diet, may reduce risk of high grade cervical lesions. In the trial, 12-week oral administration of indole-3-carbinol, a compound found in cruciferous vegetables such as cabbage and kale, was more effective than placebo in regression of precancerous cervical lesions.[48] Other studies of the association between diet and precancerous cervical lesions are more equivocal. An observational study from India which found no significant difference in 24-hour dietary recall between healthy women and women presenting with LSIL or HSIL.[47] We speculate that our finding that a healthy diet was more common in women with high grade precancerous lesion may be due to age-related differences in diet, that were not adequately controlled for in analysis.

Our study had several limitations. Due to the retrospective nature of the study, we were unable to evaluate the influence of explanatory factors on progression of precancerous lesions, or report on the frequency of regression. Assessment of diet was based on 1-week recall, and may not have provided a precise estimate of actual food intake. Finally, our sample size was relatively small and may not have allowed for estimation of moderate to small effect sizes.

CONCLUSION

The oncogenic HR HPV 16/18 strain is an important risk factor for precancerous cervical lesions in Kenya, with risk greatest among older women. The recent roll-out of the HR HPV immunization program in Kenya may reduce risk of cervical cancer in the coming years, but will not benefit the large number of Kenyan women who are already infected. Given the high costs associated with universal cervical can-

cer screening, targeted screening of high-risk women seeking reproductive health services should be considered.

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REFERENCES

1. World cancer research fund. Cervical cancer statistics. https://www.wcrf.org/dietandcancer/cancer-trends/worldwide-cancer-data. Accessed March 2019
2. Torre LA, Bray F, Siegel, RL, et al. Global cancer statistics. CA Cancer J Clin. 2012; 65:87–108[PubMed]; [Google Scholar]
3. World Health Organization, Geneva. Statistics in Cervical Cancer infections 2018. https://www.who.int/cancer/prevention/screening/cervical-cancer/en/ Accessed July 2019
4. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018; 68(6): 394-424[PubMed]; [Google Scholar]
5. McCredie M, Sharples K, Paul C, et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. Lancet Oncol. 2008; 9(5):425-434. [PubMed]; [Google Scholar].
6. Getinet M, Gelaw B, et al. Prevalence and predictors of Pap smear cervical epithelial abnormality among HIV positive and negative women attending gynecological examination in cervical cancer screening centre at Debre Markos referral hospital, East Gojjam, Northwest Ethiopia. BMC Clin Pathol. 2015; 15 (16).[PubMed]; [Google Scholar].
7. Blake K, Ottenbacher A, Finney-Rutten L. Predictors of Human Papillomavirus awareness knowledge: Gaps and Opportunities for Targeted Communication Strategies. Am J Prev Med. 2015; 48(4):402–410.[PubMed]; [Google Scholar].
8. Auwal IK, Aminu M, et al. Prevalence and high-risk Human Papilloma infections among women attending gynecology clinics in Kano, Northern Nigeria. Bajopas. 2013; 6(1). [Google Scholar].
9. Memiah P, Mbuthia W and Kiiru G. Prevalence and risk factors associated with pre- cancerous cervical cancer lesions among HIV infected women in resource limited settings. Aids Res Treat. 2012; doi:10.1155/2012/953743.[Pubmed.]; [Google Scholar].
10. Muitta E, Were T, Kebira AN, and Muhoho N. Atypical cervical cytomorphologic predictors: a descriptive study of pre-cervical cancer patients of low education in Kenya. Pamj.2019;33(124):15753. [Google Scholar].
11. Cancer research UK. Cervical cancer risks and causes.www.cancerresearch.uk.org Accessed23 March 2019
12. Massad LS, Ahdieh L, Benning L, Minkoff H, Greenblatt RM, Watts H, Miotti P, Anastos K, Moxley M, Muderspach LI, Melnick S. Evolution of cervical abnormalities among women with HIV-1: evidence from surveillance cytology in the women's interagency HIV study. J Acquir Immune Def Synd. 2001; 27(5). [PubMed];[Google Scholar].
13. Fearon KC, Voss AC, Hustaed DS, and Cancer Cachexia Study Group. Definition of cancer cachexia: effect of weight loss, reduced food intake, and systemic inflammation on functional status and prognosis. Am J Clin Nutr. 2006; 83(54): 1345–1350. [PubMed]; [Google Scholar].
14. Argiles JM, Lopez-Soriano FJ, Toledo M, Betancourt A. and Serpe R. The cachexia score (CASCO): A new tool for staging cachectic cancer patients. Jour Cachexia sarcopenia Musc. 2011; 2(7): 93-87. [PubMed]; [Google Scholar].
15. Burd, M. E., (2003) Human papillomavirus and cervical cancer. Canc Amer Clin micro Rev 16(1), 1-17. [PubMed]; [Google Scholar].
16. American Cancer Society. Cervical Cancer diagnosis, treatment and prevention. http://www.cancer.org/cancer/cervicalcancer/index. Accessed July 2019
17. Vinh-Hung Vincent, Bourgain C, Vlastos Georges. Prognostic value of histopathologyand trends in cervical cancer: A SEER population study BMC cancer. 2007; 7(1): 164.[PubMed]
18. Nayar R and Wilbur DC. The Bethesda system for reporting cervical cytology: A historical perspective. Acta Cytologica. 2017; 61: 359-372[PubMed]; [Google Scholar]
19. Ferris N, Daron G, et al. American Society for Colposcopy and Cervical Pathology. Modern Colposcopy Textbook and Atlas. 2nd edition. Kendall-Hunt Publishing Co. Dubuque. 2004.[Google Scholar].
20. Nakuru DSP-District strategic plan (2005–2010). Implementation of the national population policy for sustainable development proposal report. http://www.mudandwood.com/nakuru-district%20strategic-plan-2005-2010.pdf. Accessed March 2019
21. Rajab J and Muchiri L. Cancer registry in two counties: Cancer/HIV linked population-based registries in Embu and Nakuru counties,2014. https://www.kemri.org/KASH/ojs-2.4.8-1/index.php/KCAB/article/view/19/0. Accessed March 2019
22. Were E, Nyaberi Z, and Buziba N. Integrating cervical cancer and genital tract infection screening into Mother Child and Family planning clinics in Eldoret Kenya. AfrHealSc. 2010; 10(1): 58-65. [PubMed]; [Google Scholar].
23. Ngugi CW, Hamadi B, Muigai AW, and Wanzala P. Factors affecting uptake of cervical cancer early detection measures among women in Thika Kenya. Hlth Care Wom Int. 2012: 3(7):95-113. [PubMed]; [Google Scholar].
24. Shim JS, Kyungwon O and Kim HC. Dietary assessment methods in epidemiologic studies. Epidemeolhealth. 2014; 36(8). [PubMed]; [Google Scholar]
25. Hills AP, Mokhtar N, and Byrne NM. Assessment of physical activity and energy expenditure: an overview of objective measures.2014: doi: 10.3389/fnut.2014.00005. [PubMed]; [Google Scholar].
26. Liming Bio. Pre-cervical cancer HPV-16/18 Antigen rapid test. http://www.limingbio.com/uploadfile/2018/0509/20180509035657649.pdf. Accessed March 2019.
27. Hughes HE and Dodds TC. Handbook of diagnostic cytology. 5th edition, E & S Livingstone LTD. 1968; E & S Livingstone ISBN 10: 0443005605. [Google Scholar].
28. Hirschowitz Lynn, Nucci M, Zaino Richard. Problematic issues in the staging ofendometrial, cervical and vulval carcinomas. Histopathology. 2013; 62(1):176-202.[PubMed]; [Google Scholar]
29. Microsoft, office version 2010. https://products.office.com/en/office-2010. Accessed March 2017
30. IBM, SPSS 21.0.1, 2010. https://www.ibm.com/account/reg/signup?formid=urx-19774. Accessed March 2017
31. International Collaboration of Epidemiological Studies of Cervical Cancer, Appleby P, Beral V, et al. Carcinoma of the cervix and tobacco smoking: collaborative reanalysis of individual data on 13,541 women with carcinoma of the cervix and 23,017 women without carcinoma of the cervix from 23 epidemiological studies. Int J Cancer. 2006;118: 1481-1495.[PubMed]; [Google Scholar].
32. International Collaboration of Epidemiological Studies of Cervical Cancer, Appleby P, Beral V, et al. Cervical cancer and hormonal contraceptives: collaborative reanalysis of individual data for 16573 women with cervical cancer and 35509 women without cervical cancer from 24 epidemiological studies. Lancet. 2007; 370 (9599): 1609-1621.[PubMed]; [Google Scholar].
33. Domfeh AB, Wiredu, EK, et al. Cervical Human Papillomavirus infection in Accra, Ghana. Ghana Med J. 2008; 42 (2): 71-78.[Google Scholar].
34. Karuri JW, Muchiri LW. Conventional Pap smear and human papillomavirus DNA co-testing in HIV infected women attending comprehensive care center in Kenyatta National Hospital. KNH publication. 2014.http://erepository.uonbi.ac.ke/handle/11295/94689. Accessed March 2017
35. Mwaka AD, Okello ES, et al. Symptomatic presentation with cervical cancer in Uganda: A quantitative study assessing the pathways to diagnosis in a low-income country. BMC. 2015; 15(15).[PubMed]; [Google Scholar].
36. Krucik GT. Clinical reproductive health abnormalities review: The University of Texas MD Anderson Cancer Center-Health line Editorial Team Review.https://www.healthline.com/health/vaginal-tumors#risk-factors. Accessed September2019
37. Oriel KA and Schrager S. Abnormal Uterine Bleeding. Ameri Fam Phys.1999. [PubMed]; [Google Scholar].
38. Boardman CH, Matthews KJ, et al. Cervical cancer review Medscape scripts. https://emedicine.medscape.com/article/253513-overview. Accessed Septem-

ber 2019

39. Brisson JK, Morin M, et al. Risk factors for cervical intraepithelial neoplasia: Differences between low and high-grade lesions. Am. J. Epidemiol.1994; 40:700-710.[PubMed]; [Google Scholar].
40. Muñoz N, et al. Role of parity and human papillomavirus in cervical cancer: The IARC multi-centric case control study. Lancet. 2002; 359(9312):1093-1101. [PubMed]; [Google Scholar].
41. Jensen KE, Schmiedel S, et al. Parity as a cofactor for high-grade cervical disease among women with persistent human papillomavirus infection: A 13-year follow-up Br J Cancer. 2013; 108(1): 234-239. [PubMed]; [Google Scholar].
42. Williams MA. Risk factors for invasive cervical cancer in Kenyan women. Int J Epidemiol. 1994; 23(5), 906-912.[PubMed]; [Google Scholar].
43. Mwaka AD, Orach GC, et al. Awareness of cervical cancer risk factors and symptoms: Cross-sectional community survey in post-conflict Northern Uganda. Health Expect.2016; DOI: 10.1111/hex.12382.[PubMed]; [Google Scholar].
44. Burkett BJ, Peterson CM, et al. The relationship between contraceptives, sexual practices and cervical human papillomavirus infection among a college population. Jour Clin Epidemiol. 1992; 45(11): 1295-1302.[PubMed]; [Google Scholar].
45. Ashour AA, Verschraegen CF, et al. Paraneoplastic syndromes of gynecologic neoplasms. J Clin Oncol. 1997; 15(3): 1272-1282. [PubMed]; [Google Scholar].
46. Mantovani G, Maccio A, et al. Cancer-related cachexia and oxidative stress: Beyond current therapeutic options. Expert Rev Anti-Cancer Ther. 2013; 3(13): 381-392.[PubMed]; [Google Scholar].
47. Labani L. Food consumption pattern in cervical carcinoma patients and controls. Indian J Med Paed Oncol. 2009; 30(2): 71-75.[PubMed]; [Google Scholar].
48. Bell MC. Placebo-controlled trial of indole-3-carbinol in the treatment of CIN Gynecologic Oncology. 2000; 78(2):123-129.[PubMed]; [Google Scholar].
49. Bouvard V, and Loomis D. Carcinogenicity of consumption of red and processed meat. Lancet oncology. 2015; 16 (16): 1599-1600.[PubMed]; [Google Scholar].

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