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Factors Associated with High-Risk HPV Positivity Among Female Sex Workers and Single Mothers in Zambia

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B.S.
Clemson University
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Thesis Committee Chair: Kristin Wall, MS, PhD

An abstract of A thesis submitted to the Faculty of the Rollins School of Public Health of Emory University in partial fulfillment of the requirements for the degree of Master of Public Health in Epidemiology
2022

Abstract

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By Benjamin O'Connell

Introduction: HPV is the most common STI in the world with millions of active cases at any given time. Most of these infections are cleared without issue, but some high-risk HPV (hrHPV) types are known to both cause warts and induce the development of cancer at or around its infection site. Because of HPV's high prevalence and propensity to cause cancer, it is routinely listed as one of the primary causes of cervical, anal, and oropharyngeal cancer. Even though a safe and effective vaccine has already been developed, its high cost and difficult shipping and administration have left many nations, especially in lower- and middle-income countries, unprotected. However, Zambia has run its government-sponsored HPV vaccination program for adolescents for nearly a decade, and the benefits should be forthcoming as those individuals grow up. Still, HPV remains a large obstacle for the foreseeable future.

Methods: Many exposures were recorded from a group of HIV-negative female sex workers and single mothers in Zambia. A preliminary simple test of association, either a chi-square test or t-test, was used on each variable to narrow down the choices. Variables that were statistically significantly (alpha 0.05) associated with hrHPV positivity in bivariate analyses (using Chi-square (or Fisher's exact) tests and t-tests, as appropriate) were entered into a Poisson regression model.

Results: In this cohort with very high hrHPV prevalence (44%), there were few symptoms of HPV reported. Pain during urination (prevalence ratio [PR] = 1.99), visual inspection with acetic acid (VIA) positivity (PR = 2.52), and changing absorbent material during menstruation in a bathroom instead of a private room (PR = 1.27) were statistically significantly associated with hrHPV infection in a multivariable model. VIA testing showed encouraging signs of reliability when cross-tabulated with hrHPV infection.

Conclusions: The results of this analysis can be used for more targeted studies into hrHPV in Zambian women. Regular screenings even when VIA tests are the only screening methods available, are recommended.

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1. Introduction

Basics of HPV

Human papillomavirus (HPV) is the most common sexually transmitted infection (STI) in the world today. Estimated numbers of active cases are in the hundreds of millions, with millions of new cases suspected each year (Sanjosé et al., 2007). The virus is present in all regions of the world. Prevalence tends to be higher in developing nations with some regions, such as central Asia, reaching a prevalence of over 45% in the adult population (Kombe Kombe et al., 2020). Globally, HPV prevalence is slightly higher in men when compared to women. This gap is thought to be largely due to societal factors rather than biological factors (Partridge and Koutsky, 2006). The virus is primarily transmitted through sexual contact (vaginal, anal, or oral), although skin-to-skin transmission is possible. It can also be transmitted from mother to child.

The HPV virus infects basal epithelial cells, but the location of the infection can vary between strains. Mucosal strains will infect moist linings of the body such as the cervix or anus while cutaneous strains infect the skin (Burd and Dean, 2016). Most cutaneous HPV infections are harmless, and the infection can be cleared before any symptoms develop. However, a small portion of cases, about 10%, lead to the formation of warts around the site of infection. These warts are generally treatable and fade over time (CDC, 2021). The majority of mucosal infections are also harmless, but mucosal HPVs have a higher risk of leading to cancer or precancerous conditions when compared to cutaneous HPVs.

HPV belongs to the family *Papillomaviridae*, a family of small, non-enveloped double-stranded DNA viruses.

HPV Strains and Cancer

As with many highly contagious viruses, several strains of HPV have developed over time. Currently, there are over 150 identified strains and even more that are yet to be discovered. Many of these strains are known to cause cancer. In fact, HPV causes more cancer in women than all other infectious agents combined (Global Cancer Observatory, 2018). HPV-related cancers tend to appear around the site of infection, commonly in the cervix, mouth, oropharynx, anus, and penis. While cancers can form in any site of infection, HPV is most commonly associated with cervical cancer and oropharyngeal cancer. Over 70% of each of these cancers stem from HPV infections with some estimates placing the burden as high as 90%. Thus, limiting HPV infections is thought to be a major goal in the fight against cancer. Cervical cancer is the fourth most common and fourth most deadly form of cancer in women, so HPV vaccination campaigns potentially prevent thousands of cancer diagnoses each year (Bray et al., 2018).

Some strains that are highly associated with cancer development are noted as hrHPV (high-risk HPV) strains, include strains 16, 18, and 45. While HPV infection can have other symptoms such as genital warts, carcinogenesis is by far the most impactful and concerning (Chan et al., 2019). HPV-related cervical carcinogenesis stems from a deregulation of the cell cycle in the infected basal cells. There are multiple confirmed viral processes that interrupt the cell cycle, but the process most commonly associated with HPV is the translation of viral protein E6. In the most widely recognized carcinogenic path, E6 binds with EA6P, a cellular protein, and the dimeric complex then proceeds to bind with p53, creating a trimeric complex (Szymonowicz

and Chen, 2021). p53 is renowned as a crucial protein for regulation of the cell cycle, and, when bound to E6 and EA6P, it cannot properly do its job as intended (Hernández Borrero and El-Deiry, 2021). Without p53 regulating the cell cycle, cellular growth and division continue unchecked. This can lead to tumor formation.

HPV Vaccines

Gardasil, the first widely available HPV vaccine, was released in 2006. Over time, other vaccines, including newer versions of Gardasil, have been introduced and cover a wider range of strains. These vaccines have been shown to be extremely safe and offer long-lasting protection. In some instances, immunity to HPV infection has been shown to last over a decade without boosters or supplementation (Markowitz & Schiller, 2021). However, HPV vaccines are not useful as a treatment, so they must be given before exposure to the virus. Because the virus is spread through sexual contact, it is recommended for children to get the vaccine before they are sexually active. Currently, WHO advises parents to have their children vaccinated between ages 9 and 14 (World Health Organization, 2011). Because HPVs are constantly changing, vaccination efforts must be knowledgeable about which strains are dominant and/or dangerous. Vaccinating against every known strain is not feasible, so decisions have to be made regarding which strains to target. The current version of Gardasil, Gardasil-9, was released in 2016 and targets 9 unique HPV types. Included in these 9 are types 16 and 18, widely regarded as the two most dangerous types, among others (CDC, 2021). Unfortunately, the HPV vaccine is relatively expensive compared to other routine vaccinations. Even without factoring shipping,

storage, or administration, a single 3-dose series can cost upwards of $700 dollars. In wealthier nations, vaccination efforts have been mostly promising despite obstacles such as stigma and physician complacency. However, some low-resource areas are unfortunately unable to afford enough doses to sufficiently protect their population (Liu et al., 2012). Thankfully, while vaccine hesitancy has been a problem in the past (in 2014, under 60% of children had received their full vaccine regiment by 1 year old), acceptance of vaccines has greatly risen in Zambia in recent years. A survey conducted by Pugliese-Garcia et al. in 2018 found that 93% of respondents planned to vaccinate their children. Some Zambians still refused to vaccinate based on prior vaccination experiences, religious beliefs, or mistrust in the science behind vaccination, but the progress is exciting nonetheless (Pugliese-Garcia et al., 2018).

HPV Prevention in sub-Saharan Africa

Sub-Saharan Africa has some of the highest HPV prevalence in the world. Often, these nations have limited resources and health investigations or interventions cannot be as thorough as healthcare workers would like them to be (Kombe Kombe et al., 2021). Even though an effective HPV vaccine has been approved since 2006, only 17 out of 46 sub-Saharan African countries have implemented national programs to promote and distribute HPV vaccines as of 2019 (Amponsah-Dacosta et al., 2020). In fact, one study estimates that only 1.2% of sub-Saharan African women between 10 and 20 years old have fully completed their vaccination series (Bruni et al., 2016). In Zambia, a vaccine program began rollout in early 2013. As mentioned, the attitude towards vaccines in Zambia has gradually become more accepting

(Pugliese-Garcia et al., 2018). Unfortunately, rates of cervical cancer have continued to climb despite this intervention (Kalubula et al., 2021). While the vaccine program has not made an immediate impact on cervical cancer prevalence in Zambia, a number of outside factors contribute to this continued rise. A successful vaccination campaign should show increasing returns as time goes on.

Two key roadblocks in Zambia's HPV prevention efforts are a high prevalence of HIV and a lack of time since the intervention began (Mayuni 2022). In addition to the HPV epidemic, Zambia also struggles with a very high prevalence of HIV positivity. An estimated 12% of the 15-49 year old population is infected with HIV, although new infections have been decreasing in recent years (Okoye et al., 2021). Zambian women have a significantly higher prevalence of HIV than Zambian men. HIV is known for weakening the body's immune system and making it harder to clear other infections, so it stands to reason that an extremely common virus like HPV will be very difficult to eliminate. Not only is HPV positivity increased by HIV, but HIV positivity also correlates with a likelihood of developing cervical cancer (Okokye et al., 2021). It's clear that cervical cancer and HPV positivity are intertwined with other disease prevention efforts.

Time is also a crucial component in the fight against HPV. The HPV vaccine is not effective as a treatment, so individuals who have already been infected don't receive the same benefit as those who are vaccinated earlier. Additionally, carcinogenesis usually takes time to appear after HPV infection. Even if a woman is infected with a high-risk strain at age 19, it might be years before signs of cancers can be seen, if any develop at all. The HPV vaccine is primarily recommended for adolescents, and adolescents are not typically at risk for HPV-related

cancers. Once these vaccinated children age into their twenties and thirties, the benefit of vaccination should be easy to see.

Lack of HPV testing and cervical cancer screening in Zambia continues to be problematic. Testing for viral DNA is only used in about 10% of cases due to budget restrictions, and only 16.4% of women between the ages of 16 and 69 had ever been screened for cervical cancer (WHO, 2020). The primary method for both HPV testing and cervical cancer screening in Zambia is the visual inspection with acetic acid (VIA) test. The VIA test is extremely simple. A few drops of 5% acetic acid are placed on the area to be screened, and if the application site changes to an opaque white, the test is positive. Acetic acid reacts with certain nuclear proteins to turn white, so aggressively dividing and growing cells will have a stronger color change. While the test may seem rudimentary, the value it provides at such a low cost is exceptional. When compared to colposcopy diagnoses for cervical cancer, VIA testing had a sensitivity of 85% and a specificity of 69% (Ardahan and Temel 2011). An obvious drawback of the VIA test is that it is unable to truly detect HPV infection; it is used as an indicator of cancerous or precancerous conditions. A viral DNA test is more definitive on a patient's HPV status, but without a treatment available for HPV, the only real benefit is knowing one's status for the future.

2. Methods

Population

The population for this analysis was originally recruited for a study focused on female genital schistosomiasis; this thesis uses this study for secondary data analysis regarding hrHPV. Participants were recruited as part of a prospective cohort of female sex workers and single mothers in the Zambian cities of Lusaka and Ndola. A subset of 498 women with complete hrHPV data are included from the original larger cohort. Study participants reported regularly for both physical exams and laboratory tests. The healthcare professionals involved in examining the study participants were both aware of the study and active in its development.

Study Design

This analysis uses cross-sectional data. The primary study for this cohort is ongoing, so only the most recent visit from each participant was included in the case of multiple visits. During participants' scheduled appointments, trained healthcare professionals administered numerous medical tests and examinations. Participants also completed surveys in both written and spoken formats. Women without complete hrHPV data were not included in the analysis. The following HPV types were considered to be high risk: 16, 18, 45, 31, 33, 35, 39, 52, 58, 51, 59, 56, 66, and 68.

Because the purpose of this analysis is to find factors associated with hrHPV positivity, a wide range of variables were included. These variables cover personal information (ex: age, city), medical information (ex: current STIs, reports of pain), and lifestyle habits (ex: recent

partners, hygiene practices). No variable was given any preference regarding inclusion in modeling.

Analysis

All analyses were done in SAS 9.4. Tests of bivariate association between covariates and hrHPV were performed. For categorical variables, we used Chi-square tests, or Fisher's exact tests, as appropriate. For continuous variables, we used t-tests. Variables with a resulting bivariate p-value less than 0.10 were considered for inclusion in a multivariable model. Initially, two separate methods of modeling were considered: the log-binomial regression and Poisson regression with robust variance estimates. Hower, the log-binomial model had very questionable convergence. Thus, it was discarded in favor of the Poisson model. To obtain prevalence ratios, the estimates from the Poisson model were exponentiated.

3. Results

Note: Larger tables can be found starting on page 18

Out of the original cohort, 498 participants had complete HPV data. Of these 498 participants, 199 (44%) were infected with one or more high-risk HPV types (Table 1). After the initial round of association testing, only 11 variables had p-value smaller than 0.10. Among these 11 variables were “active chlamydia”, “active gonorrhea”, and “active chlamydia or gonorrhea”. Due to concerns over model convergence and collinearity, “active chlamydia or gonorrhea” was not included as it was potentially redundant. Additionally, “leaking urine while walking or exercising” was also removed due to high collinearity. The Poisson regression model found three of the modeled variables to be statistically significant: location of changing of absorbent materials, pain during urination, and a positive VIA test (Table 4).

We also made a crosstabulation between age (in tertiles) and VIA status but did not find any statistically significant association (Table 3).

Table 1: **Prevalence of VIA and hrHPV positivity**

Variable of interest	**N missing**	**N**	**%+**
VIA+	11	128	26%
hrHPV+	0	199	44%
Type 16	0	36	7.9%
Type 18 and 45	0	40	8.8%
Other hrHPV Types*	0	165	36%
hrHPV: high risk human papilloma virus, VIA: visual inspection with acetic acid			

Table 2: Association between hrHPV status and VIA status

	VIA+ (N=116)		VIA- (N=331)		Chi-square p-value
hrHPV Status					**0.001**
hrHPV+ (N=197)	63	54%	134	40%	
hrHPV- (N=250)	53	46%	197	60%	
hrHPV: high risk human papilloma virus, VIA: visual inspection with acetic acid					

Table 3: Association between VIA results and age in tertiles

	N missing	Total N= 482		VIA+ (N = 126)		VIA- (N =356)		Chi-square P-value
	16	**N**	**%**	**N**	**%**	**N**	**%**	
Age in Years (Tertiles)								0.370
≤ 25		218	45.2%	62	49.2%	156	43.8%	
26-27		86	17.8%	24	19.0%	62	17.4%	
26 ≥		178	36.9%	40	31.7%	138	38.8%	
VIA: visual inspection with acetic acid								

Table 4: Results of Poisson Regression: factors associated with hrHPV positivity

	PR	95% Confidence Limits		P-value
Number of Pregnancies (per pregnancy increase)	0.93	0.85	1.0	0.154
Age of First Pregnancy (per year increase)	0.97	0.94	1.0	0.120
Previously having a Miscarriage (versus not)	0.71	0.46	1.1	0.130
Location of Changing of Absorbent Material[#]	1.3	1.0	1.6	0.021
Leaking Urine while Coughing or Sneezing (versus not)	0.82	0.53	1.3	0.385
Pain During Urination (versus none)	2.0	1.4	2.8	<0.001
Bloody Discharge (versus not)	0.93	0.85	1.0	0.154
Positive VIA Test (versus not)	1.3	1.0	1.5	0.036
Diagnosis of Chlamydia (versus not)	1.2	0.85	1.6	0.343
Diagnosis of Gonorrhea (versus not)	1.3	0.93	1.9	0.126

PR: prevalence ratio

[#]Changing absorbent material during menstruation in a bathroom as compared to changing the material in a private room

4. Discussion

Main Findings

HrHPV in this study population was very high at 44% (Table 2). This is similar to other cohorts of sub-Saharan sex workers (Sweet et al., 2020)(Ferré et al., 2019). Sex workers are inherently at increased risk for STIs compared to the general public due to the nature of their work. HIV positive individuals have been shown to be at increased risk from HPV, especially high-risk types (Diop-Ndiaye et al., 2019).

Table 2 also shows promising results for the reliability of VIA tests. There is significant overlap between hrHPV+ and VIA+ groups and, conversely, hrHPV- and VIA- groups. Because most cervical cancer in the region is attributed to HPV, we expect these two variables to be correlated. There are still several participants that are VIA+ and HPV-, suggesting that the sensitivity of the VIA test is not perfect (Table 2). Because of the ease of use and low cost of the VIA test, I consider these results to be reassuring overall. While the test is not perfect, it is certainly worth its continued use.

Our key finding was that location of changing of absorbent materials, pain during urination, and a positive VIA test were associated with hrHPV infection. Pain during urination being associated with hrHPV positivity is logical. Genital warts or cellular damage caused by HPV infection can weaken, clog, or otherwise irritate the urethra and the surrounding tissue. Though it is typically not the primary point of infection, HPV can even infect the urethral epithelium itself (Armbruster-Moraes et al., 1993).

The most puzzling result of our analysis is the location of the changing of absorbent material during menstruation somehow being highly associated with hrHPV positivity. Study participants who changed their material in their household bathroom were at higher risk for HPV (1.04-1.55 more likely) compared to participants who changed their material in another private room. There is no obvious causal pathway between exposure and outcome. This may be a spurious finding. To expand on this finding, a study with much greater detail centered around menstrual products and HPV should be conducted.

Because the VIA test can only detect cervical damage, it is very reactive when used as a diagnostic tool. HPV-related carcinogenesis takes time, usually years after infection. Prior to preforming any analyses, we hypothesize that we would see more VIA positives in older women as they have likely had more time since their initial HPV infection for cervical damage to develop. However, we found no meaningful differences in the prevalence of VIA positivity by age (Table 3).

Interestingly, several symptoms of HPV are not associated with HPV positivity. Genital warts are the hallmark symptom of HPV, yet only three participants had vaginal warts and only one had a mass in the cervix. Because the sample population skews young (mean age is roughly 26), it is understandable that there are not many clear and obvious cases of cervical cancer due to the time component of the disease.

Limitations:

A key limitation is that the study was not to answer primary research questions about HPV. Although there is more than enough data to conduct meaningful analysis, future studies centered around HPV would be useful.

Our sample size of 498 is decently large but could be improved for increased study power. Additionally, the study population is localized to the Zambian cities of Lusaka and Ndola, limiting generalizability. Each participant is a sex worker or single mother, greatly increasing their risk for certain behaviors or infections (Kilembe et al, 2019), and also limiting generalizability.

This study is meant to provide a preliminary analysis for sorting through large numbers of exposures and finding associations with an outcome. It is useful for getting an initial footing on a topic. Causality is not part of the study results. In order to design an effective, targeted intervention, more studies are needed.

5: References

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6: Supplementary Tables

Table 5. Initial Intake Survey

	N Missing	Total N = 498 N	%	hrHPV+ (N=224) N	%	Not diagnosed with hrHPV (N = 274) N	%	P-Value*
City	0							0.17
Lusaka		270	54.2%	129	57.6%	141	51.5%	
Ndola		228	45.8%	95	42.4%	133	48.5%	
Province of Birth	2							0.66
Copperbelt		218	44.0%	86	43.2%	119	46.7%	
Lusaka		191	38.5%	79	39.7%	91	35.7%	
Other		87	17.5%	34	17.1%	45	17.6%	
Lived in a village or rural area prior to the age of 16?	1							0.24
Yes		121	24.3%	49	21.9%	72	26.4%	
No (or Unknown)		376	75.7%	175	78.1%	201	73.6%	
Do you consume tobacco (all that apply)?	3							0.79
Yes, smoking or chewing		29	5.86%	14	6.31%	15	5.49%	
No (or Unknown)		466	94.1%	208	93.7%	258	94.5%	
Age difference between you and the oldest partner you have ever had sex with?	1							0.35
< 4 years		134	27.0%	55	24.7%	79	28.8%	
5-9 years		241	48.5%	116	52.0%	125	45.6%	
>= 10 years		122	24.5%	52	23.3%	70	25.5%	
Ever used oral contraceptives for >5 consecutive years?	1							0.59
Yes		61	12.3%	30	13.4%	31	11.4%	
No, (used for < 5 years)		131	26.4%	62	27.7%	69	25.3%	
No (never used)		305	61.4%	132	58.9%	173	63.4%	

	N Missing	Total N = 498 N	%	hrHPV+ (N=224) N	%	Not diagnosed with hrHPV (N = 274) N	%	P-Value*
Ever had regular unprotected intercourse for 12 or more months without getting pregnant?	2							0.60
Yes		94	19.0%	40	17.9%	54	19.8%	
No		402	81.0%	183	82.1%	219	80.2%	
Have you ever been pregnant?	0							0.76
Yes		473	95.0%	212	94.6%	261	95.3%	
No		25	5.0%	12	5.4%	13	4.7%	
Number of pregnancies (mean, SD)	25	473		212	2.2(1.2)	261	2.4(1.2)	0.10
Age at first pregnancy (mean, SD)		435		189	18.0(2.3)	246	18.6(2.5)	0.02
History of pregnancy disturbances	25							0.47
None	33	394	84.7%	181	86.6%	213	83.2%	0.31
Pre-term birth	33	9	1.9%	4	1.9%	5	2.0%	0.98
Miscarriage	33	46	9.9%	15	7.2%	31	12.1%	0.80
Stillbirth	33	15	3.2%	9	4.3%	6	2.3%	0.23
pre-term and miscarriage		1	0.2%	0	0.0%	1	0.4%	0.36
Unknown		4	0.9%	1	0.5%	3	1.2%	
History of pregnancy disturbances (binary)	29							0.32
None or Unknown		398	84.9%	182	86.7%	216	83.4%	
One of the above (pre-term birth, miscarriage, still birth, ectopic pregnancy)		71	15.1%	28	13.3%	43	16.6%	
How often do you currently menstruate?	4			0				0.22
Once a month		367	74.3%	171	77.4%	196	71.8%	
Every 1-3 months		56	11.3%	19	8.6%	37	13.6%	
Do not menstruate (menopause)		7	1.4%	5	2.3%	2	0.7%	
Do not menstruate (breastfeeding)		24	4.9%	9	4.1%	15	5.5%	

	N Missing	Total N = 498 N	%	hrHPV+ (N=224) N	%	Not diagnosed with hrHPV (N = 274) N	%	P-Value*
Other		40	8.1%	17	7.7%	23	8.4%	
How often do you currently menstruate? (recoded)	4							0.36
Once a month		367	74.3%	171	77.4%	196	71.8%	
Every 1-3 months		56	11.3%	19	8.6%	37	13.6%	
Does not menstruate (menopause, breastfeeding, or on hormonal contraceptives that have stopped periods)		31	6.3%	14	6.3%	17	6.2%	
Other		40	8.1%	17	7.7%	23	8.4%	
Do you have any vaginal bleeding outside of menstruation days (spotting)?	2							0.48
Yes		52	10.5%	21	9.4%	31	11.4%	
No		444	89.5%	202	90.6%	242	88.6%	
What was the most commonly used absorbent material during the last 6 menstrual cycles?	0							0.70
Disposable sanitary pads		394	79.1%	181	80.8%	213	77.7%	
Reusable cloths/towel		79	15.9%	33	14.7%	46	16.8%	
Nothing, Other, Unknown		25	5.0%	10		15		
Where do you wash your reusable absorbent materials?	419							0.39
Bucket/sink/basin at home		72	92.3%	29	46.8%	43	48.3%	
I don't wash it or other		6	7.7%	33	53.2%	46	51.7%	
How often do you typically change the absorbent material on your heaviest day of menstruation?	19							0.46
Once a day		9	1.9%	4	1.5%	5	2.3%	
Twice a day		79	16.5%	41	15.6%	38	17.6%	
Three times a day or more		391	81.6%	218	82.9%	173	80.1%	
	16							0.02

	N Missing	Total N = 498 N	%	hrHPV+ (N=224) N	%	Not diagnosed with hrHPV (N = 274) N	%	P-Value*
Where do you change your absorbent material used during menstruation?								
In a household toilet		217	45.0%	111	50.9%	106	40.2%	
In a private room in the house		265	55.0%	107	49.1%	158	59.8%	
How many times a day do you wash yourself (bath/ vaginal wash) when menstruating?	0							0.74
Once a day		8	1.8%	4	2.0%	4	1.6%	
Twice a day		114	25.0%	48	24.1%	66	25.7%	
Three times a day or more		321	70.4%	143	71.9%	178	69.3%	
Other/Unknown		13	2.9%	4	2.0%	9	3.5%	
How many times a day do you wash yourself (bath/ vaginal wash) when NOT menstruating?	7							0.45
Once a day		9	1.9%	5	2.3%	4	1.5%	
Twice a day		131	27.1%	60	27.4%	71	26.9%	
Three times a day or more		343	71.0%	154	70.3%	189	71.6%	
Have you ever experienced any of the following due to your menstruating period? (Select All that Apply)								
Having to isolate from household/sexual partner	0	191	38%	88	39%	103	38%	0.7
Not allowed to handle food and/or drinks	0	115	23%	54	24%	61	22%	0.63
Not allowed to enter religious or culturally sacred spaces	0	33	7%	16	7%	17	6%	0.78
Not allowed to participate in social activities (community gatherings, commerce, etc)	0	14	3%	4	2%	10	4%	0.36
None	0	258	52%	119	53%	149	54%	0.78

	N Missing	Total N = 498 N	%	hrHPV+ (N=224) N	%	Not diagnosed with hrHPV (N = 274) N	%	P-Value*
Do you sometimes leak urine (even small drops),wet yourself, or wet your pads/undergarments?(Select all that apply)								
When you cough or sneeze	0	45	9%	15	6%	30	11%	0.10
When you bend down or lift something	0	7	1%	4	2%	3	1%	0.51
When you walk quickly, jog or exercise	0	4	1%	0	0%	4	1%	0.07
When undressing to use the toilet	0	18	4%	7	3%	11	4%	0.60
Do you sometimes have to rush to the bathroom because you get a sudden, strong need to urinate?	0							0.43
Yes		114	22.9%	55	24.6%	59	21.5%	
No or unknown		384	77.1%	169	75.4%	215	78.5%	
Do you sometimes have to rush to the bathroom because you get a sudden, strong need to urinate? (Binary)	0							0.42
Yes		114	22.9%	55	24.6%	59	21.5%	
No (or Unknown)		384	77.1%	169	75.4%	215	78.5%	
During the last 4 weeks, how bothered were you by frequent urination during the daytime hours?	0							0.11
Not at all		358	78.5%	164	82.4%	194	75.5%	
a little bit		63	13.8%	25	12.6%	38	14.8%	
somewhat/quite a bit/a great deal/a very great deal		35	7.7%	10	5.0%	25	9.7%	
History of bloody urine	0							0.91
Yes		7	1.4%	3	1.1%	4	1.8%	
No		491	98.6%	270	98.9%	221	98.2%	

History of genital ulcer	0							0.51

	N Missing	Total N = 498 N	%	hrHPV+ (N=224) N	%	Not diagnosed with hrHPV (N = 274) N	%	P-Value*
Yes		15	3.0%	8	3.6%	7	2.6%	
No		483	97.0%	216	96.4%	267	97.4%	
History of genital warts/growths	0							0.16
Yes		12	2.4%	3	1.3%	9	3.3%	
No		486	97.6%	221	98.7%	265	96.7%	
History of contact pain during intercourse	0							0.87
Yes		28	5.6%	13	4.8%	15	6.6%	
No		470	94.4%	259	95.2%	211	93.4%	
Have you ever experienced any of the following due to any genital or urinary problems? (Select all that apply)								
Having to isolate from household/sexual partner	0	11	2%	6	3%	5	2%	0.55
Not allowed to handle food and/or drinks	0	2	0%	1	0%	1	0%	0.89
Not allowed to enter religious or culturally sacred spaces	0	1	0%	1	0%	0	0%	0.37
Not allowed to participate in social activities (community gatherings, commerce, etc)	0	1	0%	0	0%	1	0%	0.37
None	0	448	90%	200	89%	248	91%	0.43
Are you having any reproductive health problems that you would like to talk to the nurse/doctor about today?	0							0.35
Yes		12	2.4%	7	3.1%	5	1.8%	
No		486	97.6%	217	96.9%	269	98.2%	
How many days have you had these symptoms?	0	12		7	7.3(10.3)	5	28(29.6)	0.11
Cystitis/dysuria?	0							0.11

	N Missing	Total N = 498 N	%	hrHPV+ (N=224) N	%	Not diagnosed with hrHPV (N = 274) N	%	P-Value*
Yes spontaneous, problem present today		6	1.2%	5	2.2%	1	0.4%	
Yes prompted, problem present today		2	0.4%	1	0.4%	1	0.4%	
No		488	98.0%	216	96.4%	272	99.3%	
Unknown		2	0.4%	2	0.9%	0	0.0%	
Cystitis/dysuria? (Binary)	0							0.09*
Unknown or No		490	98.4%	218	97.3%	272	99.3%	
Yes		8	1.6%	6	2.7%	2	0.7%	
Vaginal itching?	0							0.61
Yes spontaneous, problem present today		10	2.0%	4	1.8%	6	2.2%	
Yes prompted, problem present today		6	1.2%	4	1.8%	2	0.7%	
No		479	96.2%	214	95.5%	265	96.7%	
Unknown		3	0.6%	2	0.9%	1	0.4%	
Vaginal itching? (Binary)	0							0.69
Unknown or No		482	96.8%	216	96.4%	266	97.1%	
Yes		16	3.2%	8	3.6%	8	2.9%	
Abnormal Vaginal discharge	0							0.73
Yes spontaneous, problem present today		6	1.2%	2	0.9%	4	1.5%	
Yes prompted, problem present today		10	2.0%	6	2.7%	4	1.5%	
No		477	95.8%	214	95.5%	263	96.0%	
Unknown		5	1.0%	2	0.9%	3	1.1%	
Abnormal Vaginal discharge (Binary)	0							0.68
Unknown or No		482	96.8%	216	96.4%	266	97.1%	
Yes		16	3.2%	8	3.6%	8	2.9%	
Dyspareunia (painful intercourse)	0							0.51
Yes spontaneous, problem present today		5	1.0%	2	0.9%	3	1.1%	

	N Missing	Total N = 498 N	%	hrHPV+ (N=224) N	%	Not diagnosed with hrHPV (N = 274) N	%	P-Value*
Yes prompted, problem present today		5	1.0%	1	0.4%	4	1.5%	
No		488	98.0%	221	98.7%	267	97.4%	
Dyspareunia (painful intercourse) (Binary)	0							0.34
Unknown or No		488	98.0%	221	98.7%	267	97.4%	
Yes		10	2.0%	3	1.3%	7	2.6%	
Bloody vaginal discharge	0							0.61
Yes spontaneous, problem present today		0	0.0%	0	0.0%	0	0.0%	
Yes prompted, problem present today		1	0.2%	0	0.0%	1	0.4%	
No		494	99.2%	271	99.6%	223	98.7%	
Unknown (99)		3	0.6%	1	0.4%	2	0.9%	
Bloody vaginal discharge (Binary)	0							0.37
Unknown or No		497	99.8%	224	100.0%	273	99.6%	
Yes		1	0.2%	0	0.0%	1	0.4%	
Lower abdominal pain	0							0.65
Yes spontaneous, problem present today		6	1.2%	4	1.8%	2	0.7%	
Yes prompted, problem present today		5	1.0%	2	0.9%	3	1.1%	
No		480	96.4%	214	95.5%	266	97.1%	
Unknown		7	1.4%	4	1.8%	3	1.1%	
Lower abdominal pain (Binary)	0							0.55
Unknown or No		487	97.8%	218	97.3%	269	98.2%	
Yes		11	2.2%	5	2.2%	6	2.2%	
Acute genital ulcer	0							0.36
Yes spontaneous, problem present today		1	0.2%	1	0.5%	0	0.0%	
Yes prompted, problem present today		0	0.0%	0	0.0%	0	0.0%	
No		454	99.6%	198	99.5%	256	99.6%	
Unknown		1	0.2%	0	0.0%	1	0.4%	

	N Missing	Total N = 498 N	%	hrHPV+ (N=224) N	%	Not diagnosed with hrHPV (N = 274) N	%	P-Value*
Acute genital ulcer (Binary)	0							0.45
Unknown or No		497	99.8%	223	100.0%	274	99.6%	
Yes		1	0.2%	0	0.0%	1	0.4%	
Chronic / Recurrent genital ulcer	0							0.35
Yes spontaneous, problem present today		1	0.2%	1	0.5%	0	0.0%	
Yes prompted, problem present today		3	0.7%	2	1.0%	1	0.4%	
No		451	98.9%	195	98.0%	256	99.6%	
Unknown		1	0.2%	1	0.5%	0	0.0%	
Chronic / Recurrent genital ulcer (Binary)	0							0.33
Unknown or no		494	99.2%	221	98.7%	273	99.6%	
Yes		4	0.8%	3	1.3%	1	0.4%	
Unpleasant vaginal odor/malodorous discharge	0							0.14
Yes spontaneous, problem present today		2	0.4%	2	0.9%	0	0.0%	
Yes prompted, problem present today		2	0.4%	2	0.9%	0	0.0%	
No		491	98.6%	218	97.3%	273	99.6%	
Unknown		3	0.6%	2	0.9%	1	0.4%	
Bloody vaginal discharge (Binary)	0							0.04
Unknown or no		494	99.2%	220	98.2%	274	100.0%	
Yes		4	0.8%	4	1.8%	0	0.0%	
Pelvic/back pain	0							0.33
Yes spontaneous, problem present today		3	0.6%	1	0.4%	2	0.7%	
Yes prompted, problem present today		7	1.4%	5	2.2%	2	0.7%	
No		487	97.8%	217	96.9%	270	98.5%	
Unknown		1	0.2%	1	0.4%	0	0.0%	

	N Missing	Total N = 498 N	%	hrHPV+ (N=224) N	%	Not diagnosed with hrHPV (N = 274) N	%	P-Value*
Pelvic/back pain (binary)	0							0.33
Yes		10	2.0%	6	2.7%	4	1.5%	
No or Unknown		488	98.0%	218	97.3%	270	98.5%	
Chronic/recurrent genital warts/growths (small bump, cluster of bumps, or stemlike protrusions) on your genitalia (vulva, vagina, or anus)	0							0.34
Yes spontaneous, problem present today		4	0.8%	0	0.0%	4	1.5%	
Yes prompted, problem present today		2	0.4%	1	0.4%	1	0.4%	
No		488	98.0%	221	98.7%	267	97.4%	
Unknown		4	0.8%	2	0.9%	2	0.7%	
Chronic/recurrent genital warts/growths (small bump, cluster of bumps, or stemlike protrusions) on your genitalia (vulva, vagina, or anus) (Binary)	0							0.23
Yes		6	1.2%	1	0.4%	5	1.8%	
No or Unknown		492	98.8%	223	99.6%	269	98.2%	
Other Pain	421							0.99
None		76	98.7%	36	100.0%	40	97.6%	
Occasional lower abdominal pain		1	1.3%	0	0.0%	1	2.4%	

hrHPV: high risk human papilloma virus
*P-values are two sided from Chi-square (or Fisher's exact) tests for categorical variables, as appropriate, and t-tests for continuous variables

Table 6a: Questions Asked During Annual Follow up (Categorical Variables)

		Total N= 498		Diagnosed with hrHPV N =224		Not diagnosed with hrHPV N =274		P-Value*
	N missing	N	%	N	%	N	%	
Current pregnancy	20	26	5.4%	10	4.72%	16	6.02%	0.53
Currently breastfeeding	43	69	15.1%	31	15.27%	38	15.1%	0.84
Current contraceptive method								
Oral contraceptive pill	43	32	7.03%	15	7.39%	17	6.75%	0.79
Injection	43	163	35.8%	72	35.47%	91	36.1%	0.89
LARC: Implanon/Jadelle/Implant	43	125	27.5%	50	24.63%	75	29.8%	0.23
LARC: IUCD/Loop	43	6	1.3%	4	1.97%	2	0.79%	0.41
None/Condoms only	43	128	28.1%	61	30.05%	67	26.6%	0.41

hrHPV: high risk human papilloma virus
*P-values are two sided from Chi-square (or Fisher's exact) tests for categorical variables, as appropriate, and t-tests for continuous variables

Table 6b: Questions from Annual Follow-Up (Discrete Variables)

		Total N= 498	Diagnosed with hrHPV N =224		Not diagnosed with hrHPV N =274		P-Value*
	N missing	N	N	Mean (SD)	N	Mean (SD)	
In the last month, how many sexual partners have you had?	17	481	213	2.2 (2.0)	268	2.3 (2.0)	0.48
In the last month, how many times have you had unprotected sex?	82	416	187	2.2(3.3)	229	2.3(3.0)	0.94
In the last month, how many times have you had sex using a condom?	114	384	167	2.3(2.6)	217	2.5(2.9)	0.51

		Total N= 498	Diagnosed with hrHPV N =224		Not diagnosed with hrHPV N =274		P-Value*
	N missing	N	N	Mean (SD)	N	Mean (SD)	
Age at first sexual intercourse?	0	498	224	17.0(2.1)	274	17.3(2.4)	0.16
Last live birth weight	32	466	208	3069.8(582.5)	258	3106.2(585.4)	0.50

hrHPV: high risk human papilloma virus
* t-test for association with hrHPV positivity

Table 7a. Questions Asked During Gynecological Examination (Categorical Variables)

		Total N= 498		Diagnosed with hrHPV = 224		Not diagnosed with hrHPV = 274		P-value
	N missing	N	%	N	%	N	%	
Age (Tertiles)	0							0.23
<25		224	45.0%	110	49.1%	114	41.6%	
26-27		88	17.7%	38	17.0%	50	18.2%	
28>		186	37.3%	76	33.9%	110	40.1%	
External genitalia								
Inguinal adenopathy > 1cm 2cm unilateral	4	2	0.4%	2	1.0%	0	0.0%	0.19
Inguinal adenopathy > 1cm 2cm bilateral	1	6	1.2%	4	2.0%	2	0.8%	0.25
Ulceration	1	1	0.2%	1	0.5%	0	0.0%	0.41
Condyloma / Warts	1	0	0.0%	0	0.0%	0	0.0%	X
Tumors/nodules on the vulva/vagina	1	0	0.0%	0	0.0%	0	0.0%	X
Internal genitalia			0.0%				0.0%	
Inflammation cervix / Cervicitis	3	39	7.9%	18	8.1%	21	7.7%	0.86

Inflammation vagina	3	1	0.2%	1	0.5%	0	0.0%	0.38
Ulcer cervix	3	1	0.2%	0	0.0%	1	0.4%	0.99
Non-bloody Discharge / Pus originating from cervix	3	18	3.6%	9	4.1%	9	3.3%	0.65
Non-bloody Discharge vagina	3	61	12.3%	28	12.6%	33	12.1%	0.63
Bloody Discharge / Pus originating from cervix	3	4	0.8%	2	0.9%	2	0.7%	0.99
Bloody Discharge vagina	3	3	0.6%	3	1.4%	0	0.0%	0.05
Erosion or friability cervix	3	12	2.4%	5	2.3%	7	2.6%	0.82
Non-menstrual bleeding cervix	3	2	0.4%	0	0.0%	2	0.7%	0.20
Condyloma / Warts vagina	3	3	0.6%	1	0.5%	2	0.7%	0.69
Tumors/nodules on the cervix	4	1	0.2%	0	0.0%	1	0.4%	0.99
VIA Positive	16	126	26.1%	72	32.7%	54	20.6%	>0.01
hrHPV: high risk human papilloma virus P-values are two sided from Chi-square or Fisher's exact tests for categorical variables, as appropriate								

Table 7b: Questions Asked During Gynecological Examination (Discrete Variables)

	N Missing	**Total N = 297**	**Diagnosed with hrHPV**		**Not Diagnosed with hrHPV**		**P-value***
			N	Mean (sd)	N	Mean (sd)	0.07
Age (years)	1	497	224	26.5(4.6)	273	27.3(4.9)	
hrHPV: high risk human papilloma virus *T-test was used to generate p-value							

Table 8: Lab Results for Study Participants

		Total N= 498		Diagnosed with hrHPV = 224		Not diagnosed with hrHPV = 274		
	N Missing	N	%	N	%	N	%	P-Value*
Chlamydia	7							0.1
Yes		38	7.7%	22	10.0%	16	5.9%	
No		453	92.3 %	199	90.0%	254	94.1%	
Gonorrhea	7							0.04
Yes		30	6.1%	19	8.6%	11	4.1%	
No		461	93.9 %	202	91.4%	259	95.9%	
Chlamydia or Gonorrhea	7							0.01
Yes		62	13%	37	17%	25	9%	
No		429	87%	184	83%	245	91%	
RPR (Syphilis)	105							0.4
Yes		355	90.3 %	152	88.9%	203	91.4%	
No		38	9.7%	19	11.1%	19	8.6%	
Sperm	55							0.43
Yes		12	2.7%	4	2.0%	8	3.3%	
No		431	97.3 %	193	98.0%	238	96.7%	
Trichomonas	52							0.77
Yes		19	4.3%	9	4.6%	10	4.0%	
No		427	95.7 %	188	95.4%	239	96.0%	
Candida	13							0.21
Yes		27	5.6%	9	4.1%	18	6.7%	
No		458	94.4 %	209	95.9%	249	93.3%	
Bacterial Vaginosis (BV)	13							0.42

Yes		86	17.7 %	42	19.3%	44	16.5%	
No		399	82.3 %	176	80.7%	223	83.5%	
hrHPV: high risk human papilloma virus P-values are two sided from Chi-square or Fisher's exact tests for categorical variables, as appropriate								