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Vaginal self-sampling for HPV infection as a primary cervical cancer screening tool in a Haitian population

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Abstract

Background—Human papillomavirus (HPV) testing as primary cervical cancer screening has not been studied in Caribbean women. We tested vaginal self-collection versus physician cervical sampling in a population of Haitian women.

Methods—Participants were screened for high-risk HPV with self-performed vaginal and clinician-collected cervical samples using Hybrid Capture 2 assays (Qiagen, Gaithersburg, Maryland). Women positive by either method then underwent colposcopy with biopsy of all visible lesions. Sensitivity and positive predictive value were calculated for each sample method compared to biopsy results, with kappa statistics performed for agreement. McNemar's tests were performed for differences in sensitivity at ≥ cervical intraepithelial neoplasia (CIN)-I and ≥ CIN-II.

Results—Of 1845 women screened, 446 (24.3%) were HPV-positive by either method, including 105 (5.7%) only by vaginal swab and 53 (2.9%) only by cervical swab. Vaginal and cervical samples were 91.4% concordant (κ= 0.73 [95% CI: 0.69 – 0.77], $p < 0.001$). Overall, 133 HPV-positive women (29.9%) had CIN-I, while 32 (7.2%) had ≥ CIN-II. The sensitivity of vaginal swabs was similar to cervical swabs for detecting ≥ CIN-I (89.1% vs 87.9%, respectively, p=0.75) lesions and ≥ CIN-II disease (87.5% vs 96.9%, p=0.18). Eighteen of 19 cases of CIN-III and invasive cancer were found by both methods.

Conclusions—HPV screening via self-collected vaginal swabs or physician-collected cervical swabs are feasible options in this Haitian population. The agreement between cervical and vaginal

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samples was high, suggesting vaginal sample-only algorithms for screening could be effective for improving screening rates in this under-screened population.

Keywords

Cervical cancer; human papillomavirus; HPV self-sampling; Haiti

Introduction

Worldwide, invasive cervical cancer is the second most common cancer in women ages 15–44 years.[1] Latin America and the Caribbean have age-adjusted incidence rates of cervical cancer ranging from 20 to 80 per 100,000 women per year and account for greater than 80% of the disease burden within the Americas.[2–4] Recent World Health Organization estimates for cervical cancer incidence in Haiti from 2000 and 2012 have varied between an age-standardized rate of 24.9 and 93.9 per 100,000 women annually.[4,5]

Cervical cancer is a preventable disease caused by the sexual transmission of oncogenic types of human papillomavirus (HPV) infection.[6] In low-resource regions, barriers such as high infrastructure costs, manpower challenges, and poor patient surveillance mechanisms frequently prevent implementation of cervical cancer screening programs.[7] With recent technological advancements in cervical cancer screening methods, however, cervical cancer incidence can be significantly reduced through high-sensitivity primary screening methods that are self-administered and cost-effective.[7–13] This includes HPV testing, which can reduce the incidence and mortality of cervical cancer relative to other methods, even if performed only once in a woman's lifetime.[7]

Because HPV testing has the potential advantage of allowing self-collection of specimens, several international studies have compared self-sampling of vaginal specimens against clinician-collected cervical samples for high-risk HPV (HR-HPV) detection.[8–15] In these studies, self-sampling has been nearly as sensitive as clinician-obtained cervical samples and more sensitive than cytology for the detection of cervical intraepithelial neoplasia (CIN) for lesions of high-grade CIN-II or higher (CIN-II+).[16–19] Given the high sensitivity of HPV testing for CIN-II+ detection, the acceptability of self-sampling for patients, and the reduction in the number of clinicians required for a pelvic-based screening program, studies suggest use of vaginal self-sampling can increase access to cancer screening in resource-limited settings.[7,10,13,18]

In Haiti, physicians are relatively few, preventive health programs are limited, and the formal health care system reaches only 60% of the population.[20] In many similar resource-limited settings, cervical cancer prevention is not a priority. However, in 2011, the Haitian Ministry of Health (MSPP) declared cervical cancer prevention a national priority, and a committee was formed in 2014 to review national cervical cancer screening guidelines. As a primary screening method involving vaginal HPV self-screening is being considered by this committee as an option to increase cervical cancer screening rates and there are no existing studies in a population of Caribbean women, we sought to test the feasibility of implementing HPV screening as primary testing for cervical cancer within a cohort of

women in Port-au-Prince, Haiti. Additionally, we sought to compare vaginal self-sampling screening methods against physician-administered cervical screening methods.

Materials and Methods

Population Studied

Two clinics in Port-au-Prince, Haiti, served as the testing locations for this study. The first is a freestanding clinic which screens approximately 4,000 women annually for cervical cancer using HPV testing. The second clinic is located within a women's reproductive health facility in the city's government district and has laboratory capabilities. A convenience sample of women were recruited through direct clinic referral through a standardized process and word-of-mouth. Women between the ages of 25 and 65 years who had engaged in vaginal intercourse at least once during their lifetimes were eligible. Exclusion criteria included current pregnancy, prior hysterectomy, or active menstruation. Women excluded for menstruation were asked to return for testing after the cessation of their menses.

Ethical Considerations and IRB Approval

Trained health workers versed in the study protocol guided participants through study documents in the Haitian Creole language. Consent forms written in Haitian Creole and English were provided to participants and orally administered as needed. The study was approved by the Institutional Review Board (IRB) at the Duke University School of Medicine (Pro00031654) as well as the Misyon Sante Fanmi Ayisyen IRB in Haiti to ensure cross-cultural ethical standards were met.

Initial study visit

Participants were assigned a randomly-generated ID number, which was placed on an ID card and used for the entirety of the study and database. Participants were then met by the study nurse who oriented them to the procedures involved in the collection of two types of high-risk HPV (HR-HPV) samples: 1) self-performed samples; and 2) clinician-performed samples.

HPV testing

Both self-performed vaginal samples and clinician-performed cervical samples were obtained using a Dacron brush (Qiagen, Gaithersburg, Maryland). Nurses instructed the participants to self-collect their specimens at the clinic by inserting the brush into the vagina and rotating the brush three times. After performing self-collection, a clinician placed a vaginal speculum and obtained a cervical sample by inserting a clean brush 1–1.5 cm into the cervical os and rotating three times. All samples were placed into HPV DNA collection tubes (Specimen Transport Medium, Qiagen, Gaithersburg, Maryland) and sealed with a paraffin secured lid for storage and transport. The two samples were identified by type by differently colored stickers labeled with ID numbers and the testing date.

Diagnostics

Weekly, de-identified HR-HPV brush samples were collected from participating clinics and mailed to a pathology laboratory in Bremerton, Washington. Vaginal and cervical samples were tested for the presence of one or more of 13 high-risk HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) using the Hybrid Capture 2 High-Risk HPV DNA Test™ (HC2, Qiagen, Gaithersburg, Maryland) pool assay.[21]

Follow-up

Patients were scheduled for a return appointment to receive results of HPV testing. At that visit, HR-HPV-negative women were asked to return for follow-up screening in a year, while women who were HR-HPV-positive by either method were immediately scheduled for colposcopy and biopsy. Nurses attempted to contact women who failed to return for results and/or follow-up appointments within approximately one week of the missed appointment.

Colposcopy and biopsy

All patients with at least one HPV positive result from either vaginal or cervical samples who received these results and returned for the prescheduled follow-up visit underwent colposcopy and biopsy. Trained physicians performed colposcopies and biopsies. Single biopsies were taken from each visible lesion seen by colposcopy and by endocervical curettage if the squamocolumnar junction was not entirely visible. Visible lesion locations were recorded. Specimens were stored in vials of formaldehyde with parafilm-secured lids to prevent leakage during shipment to the diagnostic facility in Washington State.

Pathology

Cervical biopsy specimens were collected and stored in 10% neutral buffered formalin for fixation and preservation. The specimens were shipped to PAKC laboratories (Silverdale Washington), where the specimens were processed and hematoxylin and eosin (H&E) stained. After staining, whole slide images of each slide were generated using a Leica SCN400 scanning system. Each whole slide image was then uploaded to a secure cloud image server, where six pathologists with expertise in cervical pathology from PathForceDx (Bremerton, Washington) rendered primary diagnoses via whole slide images accessed using Simagis viewing software (Smart Imaging Technologies, Houston, TX). Diagnoses were rendered using the Lower Anogenital Squamous Terminology (LAST) 2012 consensus recommendations.[22] Results were given with a two-tiered classification system (LGSIL and HGSIL) for low-grade and high-grade squamous intraepithelial lesions with corresponding older classifications (HPV effect, CIN-I, CIN-II, CIN-III) provided for diagnostic clarification. All diagnostic reports were rendered using the cloud-based reporting system *LIS Anywhere* (Xifin corp., San Diego, California).

Treatment

Given potential loss to follow-up, a “see-and-treat” protocol was offered to women with suspicious lesions during the colposcopy examination if there was a concern about their ability to return. Patients in this group with lesions that were not consistent with invasive cancer were treated with cryotherapy in the clinic, while those with invasive cancer were

referred for other management. After biopsy results returned, women were scheduled for cryotherapy treatment, as appropriate, or were referred to the Groupe de Support Contre le Cancer for assistance with patient navigation to other treatment facilities.

Data analysis

Descriptive statistics were performed for vaginal and cervical HPV positivity, stratified by level of disease observed in biopsy samples. Sensitivity and positive predictive value (PPV) were calculated for cervical and vaginal HR-HPV assays compared to biopsy results.

Kappa statistics were performed for agreement between self-collected and clinician-collected samples. For patients who were biopsied in multiple cervical quadrants, the highest level of disease found in any of the quadrants was reported and used for analysis. Differences in sensitivity for ≥ CIN-I and ≥ CIN-II disease were compared using McNemar's test for paired samples. All analyses were considered significant at a p-value < 0.05 and conducted using STATA v.11 (College Station, Texas).

Results

Study Population

A total of 1,845 women enrolled in the study, with a median age of 41 years and age of sexual debut of 19 (Table 1). Although most women (62.4%) reported only one or two sexual partners in their lifetimes, half (50.8%) of the women's partners had children with other women. Of the women enrolled, cervical screening data are available on 1,836 women.

HPV Results

Overall, 446 women (24.3%) were HR-HPV-positive and referred for further testing (Table 2). Vaginal self-swabs resulted in a higher detection rate for HPV, with 53 women positive on only their cervical sample (11.9% of positive women) and 105 (23.5%) on only their vaginal sample. Among HPV-positive women, 288 (64.6%) tested positive by both vaginal and cervical HPV collection methods. Overall concordance between the vaginal and cervical testing was 91.4% (1678 of 1836) with good strength of agreement (κ= 0.73 [95% CI: 0.69 – 0.77], $p < 0.001$). In patients with ≥ CIN-II disease, 27 of all 32 cases with visible lesions (84.4%), including all four cases of cancer, were HPV-positive by both methods (Table 3).

HPV Screen Compared to Biopsy

A total of 75 of 446 HR-HPV-positive women (16.8%) did not return for the recommended follow-up appointment for colposcopy and biopsy. Women who did not return were younger (35.2 vs 39.5 years, $p<0.01$), had first pregnancies at younger ages (17.2 vs 20.1 years, $p<0.01$), and were less likely to be married ($p<0.05$) than women who returned. Of the remaining 371 women who returned for these appointments and underwent colposcopy, 4 had non-diagnostic biopsy results and one did not receive a biopsy. These 5 women were excluded from the analysis, yielding a final sample size of 366 women with at least one positive HR-HPV test who underwent biopsy. This included a total of 48 women (13.1% of those with biopsies) who had a positive cervical swab but negative vaginal swab, 73 women

who had a positive vaginal swab but negative cervical swab (19.9%), and 245 women who had both positive cervical and vaginal swabs (66.9%, Table 3).

Overall, 25 women (5.6%) had normal biopsy results, while 165 (37.1%) had dysplasia on biopsy. A total of 133 women (29.9%) had CIN-I disease, while 32 (7.2%) had ≥ CIN-II disease (Table 3).

The sensitivity of vaginal swabs for detecting ≥ CIN-II was 87.5% (95% CI 84.1%–90.9%) compared to 96.9% (95% CI 95.1–98.7%) for cervical swabs (Figure 1, p=0.18). The PPV for vaginal swabs for detecting ≥ CIN-II was 8.8% (95% CI 5.9–11.7%) compared to 10.6% (95% CI 7.4% – 13.7%) for cervical swabs. The sensitivity of vaginal swabs for detecting ≥ CIN-I disease was 89.1% (95% CI 85.9–92.3%) compared to 87.9% (95% CI 84.5–91.2%) for cervical swabs (p=0.75). The PPV for vaginal swabs for detecting ≥ CIN-I was 46.2% (95% CI 41.1–51.3%) compared to 49.5% (95% CI 44.4–54.6%) for cervical swabs. Both methods were highly sensitive for ≥ CIN-III disease, with 18 of 19 found by both methods and the remaining case found by vaginal swab.

Discussion

This study demonstrates the feasibility of performing HR-HPV screening as a primary cervical cancer screening modality in a low-resource, Haitian population. Women in this study volunteered to participate in vaginal self-screening for HPV. The sensitivity of HPV screening for detecting ≥ CIN-II in this study was 87.5% for vaginal samples and 96.9% for cervical samples and our kappa concordance value was similar to others reported in the literature.[16,19] The agreement between cervical and vaginal samples was high, suggesting vaginal sample-only algorithms could be implemented in this under-screened and high-risk population to improve access to cervical cancer screening.

The prevalence of HPV in this population was 24.3%. Compared to other HPV studies in low-resource populations amongst similarly-aged women, our Haitian population had an almost three-fold higher rate of HPV positivity than in a population in Mexico and had comparable rates to populations in South Africa and Tanzania.[18,23,24] Women in this study had a relatively low number of lifetime sexual partners and late age of sexual debut, minimizing the chance of spectrum bias for cervical disease. Additionally, the overall rate of HPV positivity is consistent with the rate of cervical cancer observed in Haitian women.

This difference between sensitivities in vaginal and cervical swabs for ≥ CIN-II disease is comparable to some studies with primarily healthy populations included in a recent review.[19] In this population, assuming no verification bias, screening only with HR-HPV testing vaginally and referring only HPV positive women by vaginal screen for further evaluation would have missed 12.5% of ≥ CIN-II disease and 14.2% of treatable HSIL lesions. In comparison, clinician-collected cervical HPV screening would have missed 3.5% of treatable HSIL lesions found by self-collection.

In an ideal research study, we would have evaluated HPV-negative women with colposcopy and random cervical biopsy to eliminate verification bias; however, this was deemed unacceptable by our clinical partners. Performing corrections for verification bias per Begg

and Greenes on our sample yields sensitivities for ≥ CIN-II of 22.3% for vaginal and 63.7% for cervical specimens with specificities of 78.7% and 82.9%; however, this excludes all women who were HPV-negative by both samples.[25,26] As a result, these corrections differ markedly and overcorrect compared to studies in which women with HPV negative results by HC2 were also evaluated, presumably because women testing positive by only one sample differ clinically regarding cervical pathology than women negative by both samples.[8,27,28] In studies by Belinson et al. and Holanda et al. in which HPV-negative women underwent colposcopy and biopsy, sensitivities for vaginal samples were >83% while those for cervical samples were >88%.[8,27]

Even though cervical samples have higher sensitivies for CIN-II+ detection, if programs that implemented vaginal swabs increased the overall rate of screening given the insufficiency of current infrastructure to provide clinician-based cervical sampling, more disease may be detected using vaginal swabs compared to cervical swabs. Furthermore, the sensitivity of HPV screening by vaginal swabs is higher than conventional cytology, which has a sensitivity of approximately 60% and is the current standard of care in Haiti.[14,17,19,29] Additionally, the overall acceptability of this self-sampling approach makes it appealing for use in remote, under-screened communities.

As we have developed a relationship with a national network of women's health facilities initially founded for HIV care (FOSREF, or Fondation pour la Santé Reproductrice et l'Education Familiale), we believe self-collection of vaginal swabs based in these available clinical settings represents a feasible next step for implementing cervical cancer prevention efforts. Similar integration of cervical cancer screening and treatment has been successfully added to existing HIV clinic infrastructure in other low-resource settings.[30] Thereafter, expanding screening further with trained community health workers referring HPV-positive women to existing clinic infrastructure could then more efficiently use available health resources via task shifting.[31] Such efforts to utilize community health personnel to increase cervical cancer screening have been successful in low-resource settings and for underserved populations in developed nations.[32–34]

Our loss to follow-up among HPV-positive women was 16.8%. Women who did not return for follow-up colposcopy and biopsy were younger at the time of their first pregnancy and their clinical evaluation. They were also less likely to be married than returning HPV-positive women in our cohort, which may suggest that they have less stable social support. Targeted outreach to this population, particularly during screening intake, may increase the number of HPV-positive women ultimately receiving treatment for cervical lesions.

This study is the first to demonstrate the successful implementation of HPV self-screening in a Caribbean population. If HPV screening was instituted as the primary cervical cancer screening strategy within Haiti, the number of women requiring pelvic examination for screening may be reduced by 75%. This would enable limited public health resources to be targeted to women with the highest risk of having clinically-significant lesions. These data will be used to inform upcoming national cervical cancer screening guidelines by the MSPP.

One limitation of this study is that only women who were HPV-positive were reflexively triaged to colposcopy, as referenced above. In future studies, we will refer a subset of women with negative HPV results to colposcopy to adjust for verification bias. Additionally, the use of colposcopy in a two-visit algorithm led to a loss to follow-up rate of 16.8% of HPV-positive women, emphasizing the need for highly specific biomarkers to be used for the triage of HPV-positive women, point-of-care colposcopy techniques, screen-and-treat algorithms and development of better follow-up systems. In the absence of a rapid, highly sensitive/specific, same-day HPV screening test, targeted efforts to educate younger, single women may positively impact this attrition rate. Next, women who present for clinical examination may not be representative of the population; however, the age, sexual debut, and number of partners in this cohort indicate no unusual risk factors for cervical disease. Finally, testing for HPV was performed in the US after shipping of specimens; therefore, we are currently working to be able to perform this testing within Haiti to eliminate the need for shipping.

The major implication of the feasibility of HPV self-screening strategies in this population is that this screening methodology might be more easily disseminated in remote, rural Haitian communities than conventional methodologies involving cytology or VIA which are dependent upon the receipt of a pelvic examination. Future research will include the additional utilization of a battery-powered colposcope providing up to 8x magnification (CerviScope) compared to conventional (25x magnification) colposcopy and VIA (1x magnification) for treatment for HPV positive women.

In conclusion, HPV screening was feasible in a large population of women in a low-resource, Caribbean setting, which should allow for development of screen-and-treat strategies to optimize public health resources using HPV self-sampling.

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Conflicts of Interest and Source of Funding:

Jennifer S. Smith has received research grants and/or served on paid advisory boards for Hologic, BD Diagnostics, Trovagene and QIAGEN over the past five years. For the remaining authors, none were declared. QIAGEN (Gaithersburg, Maryland) provided HPV testing kits and specimen transport media and the Center for Aids Research (CFAR Parent Grant Number 2P30 AI064518-08) and Duke University (AI064518) provided funding for this study. The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

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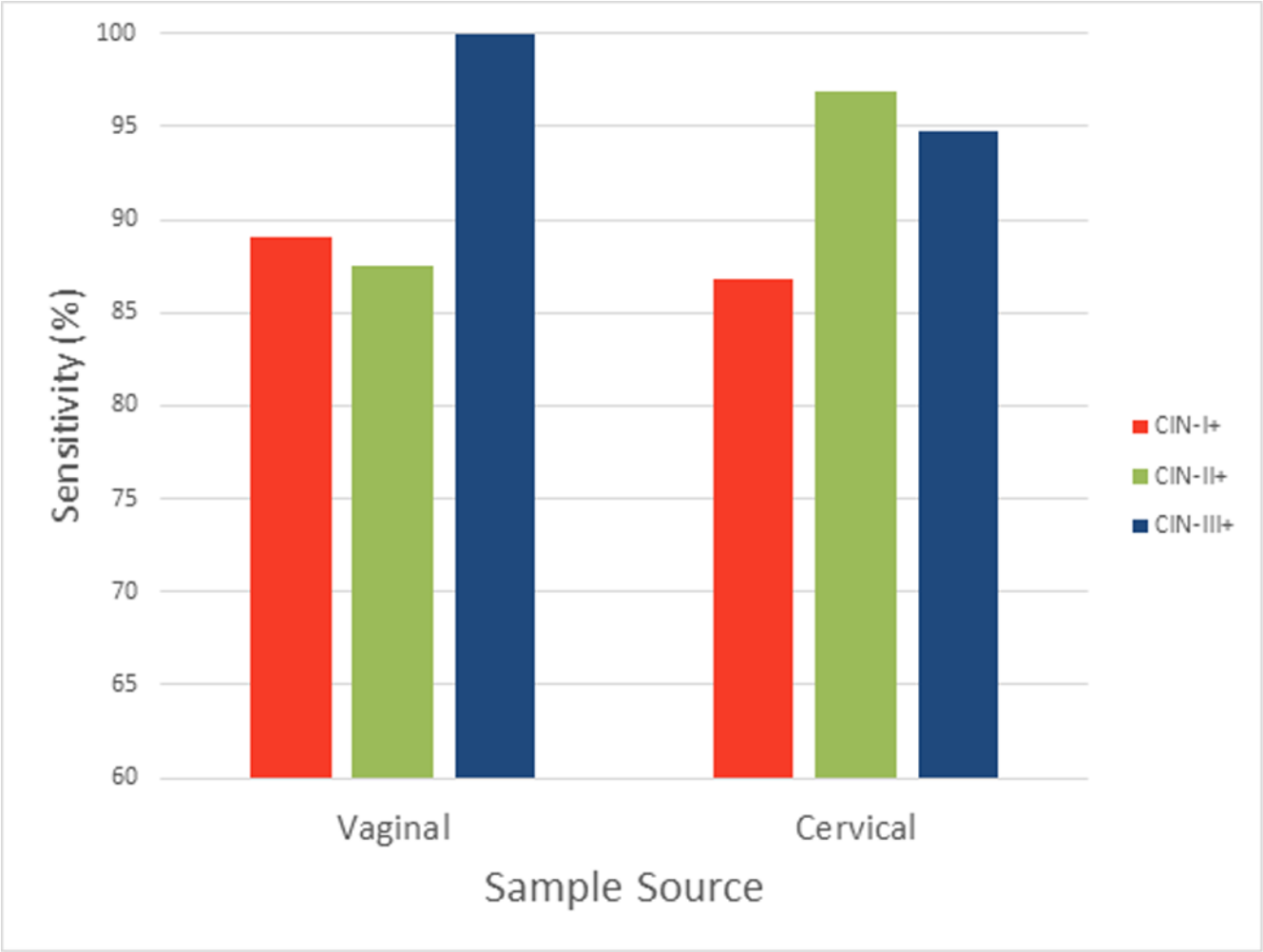

Figure 1.
Sensitivity for Detecting Different Levels of Cervical Dysplasia, by Specimen Source

Table 1

Demographics of Study Participants (n=1,836)

Age in years (interquartile range (IQR))	41 (34, 48)
Age at sexual debut in years (IQR)	19 (17, 22)
Age at menarche in years (IQR)	14 (13, 16)
Age at first pregnancy in years (IQR)	21 (18, 25)
Number of lifetime partners (SD)	2.5 (2.5)
Number of lifetime pregnancies (SD)	4.1 (2.9)
Number of vaginal deliveries (SD)	2.7 (2.3)
Number of Caesarean sections (SD)	0.2 (0.5)
Number of therapeutic abortions (SD)	0.8 (1.2)
Number of miscarriages (SD)	0.4 (0.8)
Number married (%)	936 (51.0)
Number unmarried but living with a partner (%)	533 (29.1)

IQR = interquartile range, SD = standard deviation

* All variables with interquartile ranges (IQR) represent medians, while those with standard deviations (SD) represent means.

Table 2

High-Risk HPV Results, Stratified by Anatomical Specimen Site*

HPV Result	Cervix Positive	Cervix Negative	Total
Vagina Positive	288 (15.7%)	105 (5.7%)	393 (21.4%)
Vagina Negative	53 (2.9%)	1390 (75.7%)	1443 (78.6%)
Total	341 (18.6%)	1495 (81.4%)	1836 (100.0%)

* $\kappa = 0.73$ for agreement for HPV positivity between vaginal and cervical samples

Table 3

Histologically-confirmed Biopsy Results, Stratified by HPV Detection Location

Biopsy Result	*HPV Result*[¶]			*Total HPV positive* (%)[§]
	Cervix + / *Vagina* −	*Vagina* + / *Cervix* −	*Both* +	
Normal	2 (0.4%)	13 (2.9%)	10 (2.2%)	25 (5.6%)
HPV Cytopathic Effect	28 (6.3%)	40 (9.0%)	108 (24.3%)	176 (39.6%)
CIN-I	14 (3.1%)	19 (4.3%)	100 (22.5%)	133 (29.9%)
CIN-II	4 (0.9%)	0 (0.0%)	9 (2.0%)	13 (2.9%)
CIN-III	0 (0.0%)	1 (0.2%)	14 (3.1%)	15 (3.4%)
Cancer / Invasive Carcinoma	0 (0.0%)	0 (0.0%)	4 (0.9%)	4 (0.9%)
Non-diagnostic[†]	1 (0.2%)	2 (0.4%)	1 (0.2%)	4 (0.9%)
Lost to Follow-Up	4 (0.9%)	30 (6.7%)	41 (9.2%)	75 (16.9%)
Total (%)[§]	**53 (13.1%)**	**105 (19.9%)**	**287 (66.9%)**	**445 (100.0%)**

[¶]HPV positive women were noted as having samples positive from only cervical specimens (Cervix + / Vagina −), only vaginal specimens (Vagina + / Cervix −), or cervical and vaginal specimens (Both +).

[§]One patient positive by both cervical and vaginal samples did not have biopsy performed.

[†]These biopsies were uninterpretable.