Diagnostic Test Evaluation of Urine and Clinical Swab HPV Tests for Detection of HPV DNA and Pre-Invasive Cervical Lesions in Women in Senegal, 1998 - 2001

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Abstract

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Cervical cancer remains a significant health challenge, particularly in Western Africa, where resources for screening are limited. This cross-sectional study evaluated the efficacy of urine HPV tests compared to swab HPV tests as diagnostic and screening tools for cervical cancer among 1,397 women aged 35 to 80 attending health centers in Dakar, Senegal, from 1998 to 2001. Participants underwent cytology, urine HPV testing, and clinical swab HPV testing, with follow-up biopsies for a subset. Urine samples were collected using a void catch-free method, and cervical samples were collected via cervical swabs preserved in PreservCyt. The study employed the PCR Roche Linear Array to detect 27 HPV types and compared the sensitivity and specificity of urine and swab samples.

The overall prevalence of HPV was higher in swab samples (17.8%) than in urine samples (12.9%). The sensitivity of urine testing for detecting any HPV present in swab samples was 39.5%, with a specificity of 92.9%. For high-risk HPV types, urine samples exhibited a sensitivity of 27.2% and a specificity of 98.8%. The sensitivity of urine HPV tests for detecting high-grade squamous intraepithelial lesions (HSIL) or invasive cancer was 33.3%, compared to 74.1% for swab HPV tests, though both methods showed high specificity. Age-stratified analysis (±45 years) indicated no statistical difference in the sensitivities between age groups.

This study's strengths include its large sample size, robust laboratory methodology, and the novel examination of urine and cervical swab analyses within a West African population.

Limitations include potential variability in sample collection timing and using a void-free catch method for urine sampling. Future research should focus on refining urine collection methods and implementing more advanced testing technologies to maximize screening accuracy.

Background

Cervical cancer, the fourth most common cancer in women in 2018, poses a significant public health challenge.[1] While countries with high sociodemographic indices (SDI) have seen an average annual decline in cervical cancer rates of approximately 1.72% from 1990 to 2019, the lack of feasibility surrounding cytology-based screening methods, vaccine availability and hesitancy, and other barriers have led to minimal reduction in cervical cancer rates in Sub-Saharan Africa (SSA) with one study finding the average annual percentage decrease of approximately 0.8% within the same period.[2,3] There are other factors besides lack of access that contribute to the low screening rates in many lower-middle-income countries (LMICs) like Senegal, including social stigma and misconceptions around screening. Multiple studies report women in LMICs feeling embarrassed at receiving pelvic exams as well as fear of pain related to the exams themselves. In Nigeria, a study found that women were worried about contracting an infection from the screening equipment.[4] Self-collected human papilloma virus (HPV) specimens could mitigate concerns about stigma associated with health center visits for screening. While self-collection demonstrates comparable sensitivity to provider collection for HPV testing,[5] these beliefs are mainly based on any invasive form of cervical cancer screening due to the tools used and the process of screening via a cervical swab. Urine tests are less invasive and require no tools to be used on or in the patient, which can alleviate some of these concerns and misconceptions patients have.

Despite the commencement of a national recommendation for cervical cancer screening in many countries throughout SSA, there is still a need for a drastic increase in screening across the regions. Senegal established a national recommendation for screening in 2018. However, only approximately 9% of women aged 25-65 had ever undergone cervical cancer screening in 2019, exposing a substantial gap in preventative measures, particularly concerning the widely adopted method of visual inspection with acetic acid (VIA) in Senegal.[6] The World Health Organization recently revised its screening guidelines, prioritizing HPV DNA detection over

VIA/cytology as the primary screening method.[7] However, cytology and VIA screening methods are still commonly used in Senegal and many other areas.[6] This study aimed to determine how useful urine is as a sampling method for detecting HPV infection and to assess it as a screening tool for cervical cancer screening. This assessment holds significant relevance for areas such as Senegal, where the feasibility of existing screening techniques poses obstacles, with the ultimate goal of improving accessibility and effectiveness in cervical cancer screening.

HPV is a necessary cause of cervical cancer, with 99.7% of cervical cancers originating from a persistent HPV infection.[8] In Senegal, the prevailing screening method involves \VIA\ every three years for women aged 30-69, highlighting the urgent need for alternative, accessible, and effective screening methods.[6] While VIA requires short training and is easily implementable, the method does have its disadvantages. Numerous studies have reported that HPV testing is a more sensitive screening method compared to VIA and Pap smears.[9] HPV urine tests may require health care workers to have slightly more technical/laboratory experience than VIA. Still, urine tests are relatively low-cost and less invasive, making them an attractive screening method for LMICs.[10]

Previous research, predominantly carried out in Asian and European countries, has investigated different methods of HPV testing, yielding mixed findings. While some studies demonstrated promising agreement between urine and cervical samples, others revealed limitations, such as poor detection sensitivity for low-risk HPV types. Some studies report that the increased sensitivity with high-risk (HR) HPV types could be the result of more exfoliated cervical cells in the urine, leading to higher detectability.[11] Multiple systematic reviews and studies published in recent years have concluded that urine HPV tests are a suitable alternative to clinical and self-collected swab tests and cytology, specifically when the latter are not readily available for any reason, which can be the case in LMICs, specifically in resource-poor areas.[12–14]

This study addressed multiple limitations observed in prior research. These include the small sample sizes and inadequate representation of HPV types.[15] The inclusion of a larger sample size and the focus on clinically sampled urine tests addressed these limitations, contributing to a more robust understanding of urine-based screening methods. This study centered on individuals from the Sub-Saharan African region, notably Senegal, a geographic area lacking much attention in previous research.

Determining the utility of HPV urinary tests compared to swab tests within this population provided a unique opportunity to extend the analysis to a novel population in Senegal, building upon existing studies conducted in various populations.[11,16–18] This study provided insight into the feasibility of utilizing urine tests for HPV and cervical cancer screening among older women in West Africa.

Knowledge gained from this study can inform healthcare policies, screening methods, and prevention strategies in Senegal, where cervical cancer screening is still in its early stages of implementation.[6] Increasing knowledge on the effectiveness of urine sampling for HPV and cervical cancer can contribute to overcoming barriers, reducing stigma, and enhancing women's access to screening in the region.[15] The results of this study may directly impact healthcare policies, enhance screening techniques, and reinforce preventive strategies in Senegal and other Sub-Saharan countries.

Methods

Study design and population

This research used a cross-sectional study design, with urine cytology, urine HPV, and clinical swab HPV samples collected simultaneously; biopsy collection was later performed at a follow-up visit for select participants. Using this data, we examined the effectiveness of detecting HPV DNA in urine samples compared to cervical swab samples. We also compared the utility of urine HPV tests and cervical swab HPV tests as screening tools for cervical cancer. The study

enrolled women who attended a community health clinic in Pikine and a public hospital in Le Dantec, where suspected cancer cases were referred, from 1998 to 2001. A total of 1,397 women met the eligibility criteria: individuals aged 35 to 80, not pregnant, with an intact cervix.

Data collection and measures

All data for this secondary analysis was obtained from a parent study which assessed the prevalence of specific types of HPV and cervical squamous intraepithelial lesions in consecutive, previously unscreened, West-African women 35 years or older.[19] This data was further restricted to those with valid urine and swab HPV results. Upon meeting eligibility criteria, participants conducted face-to-face interviews, providing in-depth information on demographic characteristics and reproductive history. Concurrently, health professionals performed a comprehensive general physical and detailed gynecological examination.

As mentioned, the study's initial gynecological examination included HPV and cytology tests on cervical swabs, followed by urine sample collection. A subset of 299 participants with abnormal cytologic findings and/or high-risk HPV infection proceeded to a follow-up visit, typically one to two months later, involving biopsy/histology collection. Additional tests, including HIV testing, additional swab samples for Pap smears (n=288) and HPV testing (n=271), and cervical biopsies of lesions (n=297), were conducted at this follow-up visit stage. Participants provided clinician-collected cervical cell samples via a cervical brush preserved in PreservCyt (Cytyc Corporation, Marlborough, MA). Additional clinician-collected samples for HPV testing were collected with a Dacron swab, placed in Specimen Transport Medium (STM; Digene Corporation, Silver Spring, MD), stored at -20°C, and sent to Seattle.

ThinPrep smears were generated and assessed by a cytotechnologist and a pathologist. Abnormalities were classified as normal, reactive cellular changes (normal), atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL), or squamous cell carcinoma.

Based on the study protocol, cervical biopsies were obtained utilizing colposcopy in specific participants. This subset included individuals with oncogenic HPV or cytologic indications of HSIL or more severe conditions, aiming to histologically verify the presence of the disease at the time of follow-up. The pathologist assessed the biopsy results, categorizing them as negative, showing reactive atypical alterations, or indicative of cervical intraepithelial neoplasia (CIN) grades I, II, or III, carcinoma in situ (CIS), or Adenocarcinoma in situ (AIS), invasive cervical squamous cell carcinoma (ICC), or adenocarcinoma.

A 100-µl cervical sample in STM underwent processing with ethanol precipitation, centrifugation, pellet drying, and re-suspension. HPV detection uses a polymerase chain reaction (PCR) based reverse-line strip test, testing for 27 HPV types (6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 57, 58, 59, 66, 68, 73, 82, 83, and 84). A biotin-labeled generic probe was used to detect all HPV DNA fragments. Tests that were positive for the generic probe and β-globin in both assays but negative for all type-specific tests using the Roche line blot were classified as positive but untyped (NT). HPV-negative controls were interspersed for potential contamination, and positive controls monitored the process. Each hybridization tray included one positive and one negative control. Testing was conducted by personnel unaware of the subject's medical history or cytologic diagnosis, ensuring unbiased results.

Urine samples were collected using a void free-catch method (also known as a midstream voided sample)[20], followed by centrifugation to pellet over 5 minutes. The supernatant was decanted, 1 mL of STM was added, and samples were frozen at -80°C. PCR prep/extraction procedures included PK digest, extraction, dot plot, and Roche Linear Array (RLA) extended 27-strip analysis.[17] The same criteria for classifying a sample as NT in the cervical swab analysis were also used during the urinalysis. Samples collected for urine and swab tests were classified as HR-HPV if they tested positive for the following types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 73, and 82. The data collection procedures described

aimed to capture a comprehensive dataset for subsequent sensitivity calculations, providing valuable insights into the efficacy of urinary tests compared to clinical swab tests for HPV detection and cervical cancer screening in the Senegalese population.

During the study period, additional information, including laboratory data and demographic characteristics, was collected from participants. Information such as ethnicity, age, number of pregnancies, lifetime number of sexual partners, and marital status was collected at baseline, and education level, smoking status, alcohol consumption, and HIV status were assessed at the follow-up visit.

Additional variables of interest for this study included age and HPV type; these variables were assessed to determine their potential impact on the utility of urine HPV testing. Studies have shown that older women are more likely to be screened for cervical cancer in Sub-Saharan Africa.[21] However, HPV prevalence is highest in younger women and declines with age.[22] In conjunction with differences in prevalence and screening rates, the rate of HPV clearance decreases with age, meaning older individuals are more likely to develop chronic HPV infections.[23] Because of age's association with the other variables of interest, it was evaluated as a potential effect modifier, dichotomizing subjects at age ±45. Research indicates more exfoliated cervical cells in the urine for HR HPV types, leading to higher detectability.[11] Therefore, it was hypothesized that samples that tested positive for high-risk HPV types would demonstrate higher sensitivity compared to the samples of all HPV types.

Statistical analyses

Firstly, we conducted descriptive analyses to evaluate the distribution of urine HPV for all demographic and health variables. To perform our first analysis, urine HPV and clinical-swab HPV test results were used to calculate the sensitivity, specificity, negative predictive values, and positive predictive values of urine for detecting HPV present in swab samples. This analysis was done on all HPV types collectively, all HR HPV types, and then stratified by the five most

common HR HPV types in urine (16, 18, 33, 52, and 58). Within these analyses, the swab test was considered the gold standard, and the urine HPV test was used as the clinical comparative test.

To assess the statistical significance of the binary age covariable (grouped into those less than 45 years old and those greater than or equal to 45 years old), a stratified analysis was done to see the varying effect of age on the utility of urine HPV testing. We used the Breslow-Day test to see if there is a difference in diagnostic values of HPV tests across age groups. This analysis was limited to those whose age was recorded in the study.

We also evaluated the sensitivity and specificity of urine and clinician-collected cervical tests and their use as a screening tool for detecting pre-invasive cervical cancer lesions. We used a combined histology/cytology variable as the gold standard, where cytology was used as the true disease status among our participants who do not have histology data, and this was compared to urine HPV samples and swab HPV samples separately. The combined histology/cytology variable was categorized into normal, atypical, LSIL, HSIL, ICC, Adenocarcinoma, Other Cancer, and Unsatisfactory. However, for the diagnostic test calculations, this variable was dichotomized into LSIL/Negative (Normal, CIN 1, Atypical, LSIL) and HSIL+ (HSIL, ICC) lesions with Adenocarcinoma, Other Cancer, and Unsatisfactory being removed from the analysis due to low sample size or the lack of applicability when creating the binary variable. We used contingency tables to evaluate these tests' sensitivity, specificity, and positive and negative predictive values. To further assess these tests, an Area Under the ROC Curve (AUC) was calculated to compare the overall diagnostic performance of the urine HPV test and the swab HPV test. All analyses were conducted in R software version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

A complete case analysis, in which only participants with data were included, was used to account for missingness. This approach aimed to thoroughly evaluate the effectiveness of

urine samples compared to clinical swab samples for HPV detection and cervical cancer screening in the Senegalese population.

Results

Our initial dataset consisted of 1,419 individuals who had urine HPV data available. After limiting the sample to individuals with valid urine and swab results, the total sample included 1,397 participants. Overall, study participants were an average age of 43, tended to be of Wolof origin, married in a polygamous relationship, and had received no formal education (Table 1). HIV status was collected at the time of enrollment (N = 282). Among HPV-negative individuals, 96.9% tested negative for HIV, while among HPV-positive individuals, 89.8% tested negative for HIV.

The utility of urine HPV samples compared to clinical-swab HPV samples was evaluated across various HPV types. The prevalence of HPV in swab samples overall was 248/1397 (17.8%) compared to 180/1397 (12.9%) in urine HPV samples. When we looked at the distribution of positive counts by type-specific HPV samples among our study population, swab HPV samples had higher positive HPV results in almost every HPV type except types 6, 11, and 83. The number of those who were classified as untyped was 105 out of the 209 positive counts among urine samples (50%) and 72 out of the 321 positive counts among swab samples (22%) (Figure 1). The sensitivity of detection of any HPV in urine compared to cervical swabs was 39.5% (Table 2). This remained relatively the same across the other HPV-type categories. The sensitivity for all HR HPV types combined was 27.2%. Among the five most common HR HPV types, sensitivity ranged from 20.0% for HPV 58 to 38.9% for HPV 33. Specificity was consistently high, with 92.9% for all HPV types combined and 98.8% for all HR HPV types combined. For individual HR HPV types, specificity ranged from 99.8% for HPV 16, 52, and 58 to 100% for HPV 33.

The diagnostic performance of urine HPV samples compared to clinical-swab HPV samples, stratified by age, is summarized in Table 3. For individuals under 45 years old, the sensitivity of urine HPV samples was 40.4%. The specificity was 92.6%, and for individuals aged 45 and older, the sensitivity of urine HPV samples was 37.5%, and the specificity was 93.8%. These values suggest slight variations in the diagnostic performance of urine HPV samples between the two age groups, with both showing high specificity and moderate to low sensitivity (Table 3). The Breslow-Day test showed no statistical difference across strata (X^2 = 0.03; p-value = 0.86).

When comparing urine and cervical swab samples to the combined histology/cytology results, the positive proportions of both were low in those with normal or atypical findings (<20%) (Table 4). For those with more severe abnormalities of LSIL, HSIL, and invasive squamous cancer, swab HPV positivity was considerably greater than that in urine. In participants diagnosed with LSIL, urine tests detected HPV in 37.0% of cases, compared to 48.1% for swab tests. For those with HSIL, urine tests identified 23.7% of cases as HPV positive, whereas swab tests identified a significantly higher rate of 73.7%. In cases of ICC, the positivity rates were 41.9% for urine tests and 74.4% for swab tests. In the small sample of women with adenocarcinoma, urine tests detected 25.0% of cases as HPV positive, while swab tests detected 75.0%. The analysis of urine (N = 1169) and swab (N = 1178) HPV samples, compared to histology/cytology results dichotomized as HSIL or worse (HSIL+) compared to Negative/LSIL, is presented in Table 5a and 5b, respectively. As seen in these tables, urine samples had substantially lower sensitivity, somewhat lower PPV and NPV, but slightly higher specificity compared to cervical swab samples. The urine HPV test exhibited a sensitivity of 33.3%, suggesting marginal effectiveness in detecting HSIL+ cases. Its specificity was 87.9%, demonstrating high accuracy in correctly identifying LSIL/Negative cases (Table 5a). The sensitivity of the swab HPV test was significantly higher at 74.1%, indicating a greater ability to identify HSIL+ cases correctly. The specificity was 85.9%, showing high accuracy in identifying

LSIL/Negative cases, comparable to urine samples (Table 5b). When looking at the area under the ROC Curve (AUC) comparing the diagnostic performance of the urine HPV test and the swab HPV test to the combined binary histology/cytology variable, the AUC values were 0.61 and 0.80, respectively (Figure 2). The test performance characteristics of urine HPV detection were similar when restricting analysis to those with histologic determination of cervical cancer disease status (Table 6; Appendix).

Discussion

In this study, we evaluated the efficacy of urine HPV tests compared to swab HPV tests as diagnostic and screening tools for cervical cancer among 1,397 participants. Overall, the prevalence of HPV was higher in clinician-collected swab samples (17.8%) compared to urine samples (12.9%), with swab samples demonstrating higher positive results across almost all HPV types. The sensitivity of urine HPV tests for detecting any HPV present in swabs was 39.5%, with a specificity of 92.9%, while for high-risk HPV types, sensitivity was 27.2% and specificity was 98.8%. When stratified by age, the sensitivity of urine HPV tests was 40.4% for individuals under 45 and 37.5% for those 45 and older, with high specificity in both groups. For detecting HSIL, urine tests had a sensitivity of 23.7% compared to 73.7% for swab tests, with urine tests showing a specificity of 87.9% and swab tests of 85.9%.

The study included several strengths, such as the large sample size and the inclusion of participants with a range of cervical abnormalities. The use of the PCR Roche Linear Array, known for its heightened sensitivity, further strengthened the study's methodology, allowing for the detection of 27 HPV types.[13,24] Employing both urine and swab samples provided a comprehensive comparison between non-invasive and traditional HPV DNA testing methods. The study's robust comparative approach, using both cytology/histology results and a binary classification system, offered valuable insight into the performance of the urine HPV tests.

However, there were notable limitations. The method of urine sample collection could affect the consistency of results. The study utilized a void-free catch method for urine sampling, which may yield lower detectable amounts of HPV DNA than first-void urine.[13,24] Vorsters et al. emphasized that the first-void fraction contains significantly more HPV DNA copies than the midstream fraction, affecting the sensitivity of urine tests, with the first-void urine sample containing 4.8 to 160 times more HPV DNA copies than midstream urine samples.[24] This also could explain why such a large proportion of the urine samples were untyped due to them testing positive by a generic probe but not positive by any of the type-specific tests, potentially due to lack of sufficient DNA in the sample to register as positive for a specific type. The small proportion of biopsy samples necessitated the combination of histology/cytology variables. Additionally, the study period from 1998 to 2001 precludes the evaluation of newer, more sensitive HPV tests that have since been developed, although it was before Senegal began any widespread HPV vaccination efforts, which may have impacted the relative utility of HPV testing for cervical cancer screening.[15]

Previous studies have explored the relative accuracy of urine as a diagnostic tool for pre-invasive cervical cancer lesions. Cho et al. conducted a meta-analysis and found that the overall relative sensitivity and specificity of HPV tests of urine samples compared to HSIL biopsy results were 0.84 and 1.06, respectively. They noted that the accuracy of urine-based HR HPV assays depends on factors such as urine collection time, urinary stream, sampling device, and the type of preservative used.[13]

Nilyanimit et al. evaluated a urine-based assay in a Thai population, reporting a sensitivity of 56.5% and specificity of 70.6% when using Pap smear results as a reference.[25] They highlighted the need for cautious interpretation due to variations in participant characteristics and the lack of standardized urine testing methods. Similarly, Yang et al. found an overall agreement of 77.1% for HPV status between urine and swab samples in China, with a kappa value 0.523. The agreement for HPV16/18 detection between urine and

clinician-collected samples was 91.5%. These findings are slightly lower compared to other similar studies mentioned in the paper[11]. These findings contrast our study, highlighting the challenges and limitations of urine-based testing.

This study is one of the first to investigate urine and cervical swab analyses within a West African population, a region disproportionately affected by cervical cancer and lacking essential resources and services for screening. Our findings contribute to the growing body of literature on non-invasive methods for HPV detection and highlight the potential utility of urine tests in such resource-limited settings. The relatively lower sensitivity of urine HPV tests compared to swab tests indicates that while urine tests have certain advantages, they are not yet fully equivalent to traditional methods in terms of diagnostic accuracy. This finding suggests a need for further theoretical exploration into the mechanisms behind HPV DNA shedding in urine and the factors influencing its detectability. Understanding these mechanisms could advance test sensitivity and reliability, enhancing the theoretical framework surrounding HPV detection methods.

From a public health perspective, integrating urine HPV testing into screening programs could offer significant benefits, particularly in increasing screening coverage among populations less likely to undergo traditional swab tests. This includes individuals who may find swab tests uncomfortable, culturally unacceptable, or logistically challenging. The high specificity of urine tests indicates that they effectively correctly identify those without cervical disease, which is crucial in avoiding unnecessary follow-ups and treatments. However, the lower sensitivity observed necessitates a cautious approach. Urine testing should complement rather than replace current swab-based methods until improvements are made. This dual approach could optimize screening efforts by combining the strengths of both diagnostic techniques, ensuring high accuracy while making screening more accessible.

Future research should aim to refine and standardize urine collection methods to enhance test sensitivity. Studies could explore the impact of different urine fractions, collection

times, and preservatives on the detectability of HPV DNA. Research into advanced PCR techniques and other molecular methods could also provide insights into improving the sensitivity and reliability of urine-based HPV tests. Additionally, longitudinal studies could assess the performance of urine tests over time and their effectiveness in detecting persistent infections or progression to cervical cancer. Given the rapid advancements in HPV testing technology, ongoing evaluation of new assays and comparison with established methods will be essential. Collaborative efforts across disciplines, including molecular biology, epidemiology, and clinical research, will drive these advancements.

The next steps also include further consideration of the socio-behavioral aspects of urine-based HPV testing. Investigating patient preferences, barriers to acceptance, and the potential for urine testing to increase screening uptake in underserved populations could provide valuable insights for public health strategies. Integrating qualitative research methods could help elucidate these factors, ensuring that a comprehensive understanding of patient needs and preferences informs the development and implementation of urine-based tests.

While urine HPV testing presents a noninvasive alternative, further research and development are necessary to enhance its diagnostic performance. By addressing the identified limitations and building on the strengths observed, future studies can contribute to optimizing HPV screening programs, ultimately improving cervical cancer prevention and control efforts.

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Table 1. Characteristics of Senegalese Women by Urine HPV Test Result, 1998-2001 (N = 1397)

Demographics	Negative (*n* = 1217)	Positive (*n* = 180)	Overall (N= 1397)
Ethnicity			
Wolof	605 (55.2%)	91 (56.9%)	696 (55.3%)
Pulaar	222 (20.2%)	35 (21.9%)	257 (20.5%)
Serere	106 (9.7%)	9 (5.6%)	115 (9.2%)
Sarakhole	22 (2.0%)	0 (0.00%)	22 (1.8%)
Manding	15 (1.4%)	1 (0.6%)	16 (1.3%)
Diola	22 (2.0%)	6 (3.8%)	28 (2.2%)
Bambara	31 (2.8%)	6 (3.8%)	37 (2.9%)
Other	74 (6.8%)	12 (7.5%)	86 (6.8%)
Missing	120	20	140
Age (years)			
Mean (SD)	42.9 (6.6)	42.6 (7.1)	42.9 (6.7)
Range	[35 – 80]	[35 – 72]	[35 – 80]
Missing	11	4	15
Number of Pregnancies			
Mean (SD)	7.5 (3.3)	7.0 (3.5)	7.4 (3.4)
Range	[0 – 19]	[0 – 18]	[0 – 19]
Missing	14	7	21
Lifetime Number of Sexual Partners			
Mean (SD)	1.4 (0.71)	1.7 (1.0)	1.5 (0.76)
Range	[0 – 7]	[1 – 10]	[0 – 10]
Missing	164	24	188
Marital Status			
Married – mono	441 (36.7%)	46 (26.3%)	487 (35.3%)
Married – poly	646 (53.7)	104 (59.4%)	750 (54.4%)
Widowed	56 (4.7%)	7 (4.0%)	63 (4.6%)
Divorced	50 (4.2%)	16 (9.1%)	66 (4.8%)
Concubine	0 (0.00%)	0 (0.0%)	0 (0.00%)
Single	10 (0.8%)	2 (1.1%)	12 (0.9%)
Missing	14	5	19
Education Level			
None	175 (63.2%)	48 (73.8%)	223 (65.2%)
Primary	61 (22.0%)	12 (18.5%)	73 (21.4%)
Secondary	41 (14.8%)	5 (7.7%)	46 (13.5%)
University	0 (0.0%)	0 (0.00%)	0 (0.0%)
Missing	940	115	1055
Smoking Status			
Never	222 (99.6%)	58 (98.3%)	280 (99.3%)
Current	0 (0.0%)	1 (1.7%)	1 (0.4%)
Past	1 (0.5%)	0 (0.0%)	1 (0.4%)
Missing	994	121	1115
Alcohol Consumption			
No	220 (98.7%)	58 (98.3%)	278 (98.6%)
Yes	3 (1.4%)	1 (1.7%)	4 (1.4%)
Missing	994	121	1115
HIV Status			

Negative	216 (96.9%)	53 (89.8%)	269 (95.4%)
HIV-1	4 (1.8%)	5 (8.5%)	9 (3.2%)
HIV-2	2 (0.9%)	1 (1.7%)	3 (1.1%)
Coinfection	1 (0.5%)	0 (0.0%)	1 (0.4%)
Missing	994	121	1115

[a] Column percentages do not include missing data

Figure 1. Distribution of Type-Specific Urine and Clinical-Swab HPV Samples Among Women 35-80 in Senegal, 1998-2001

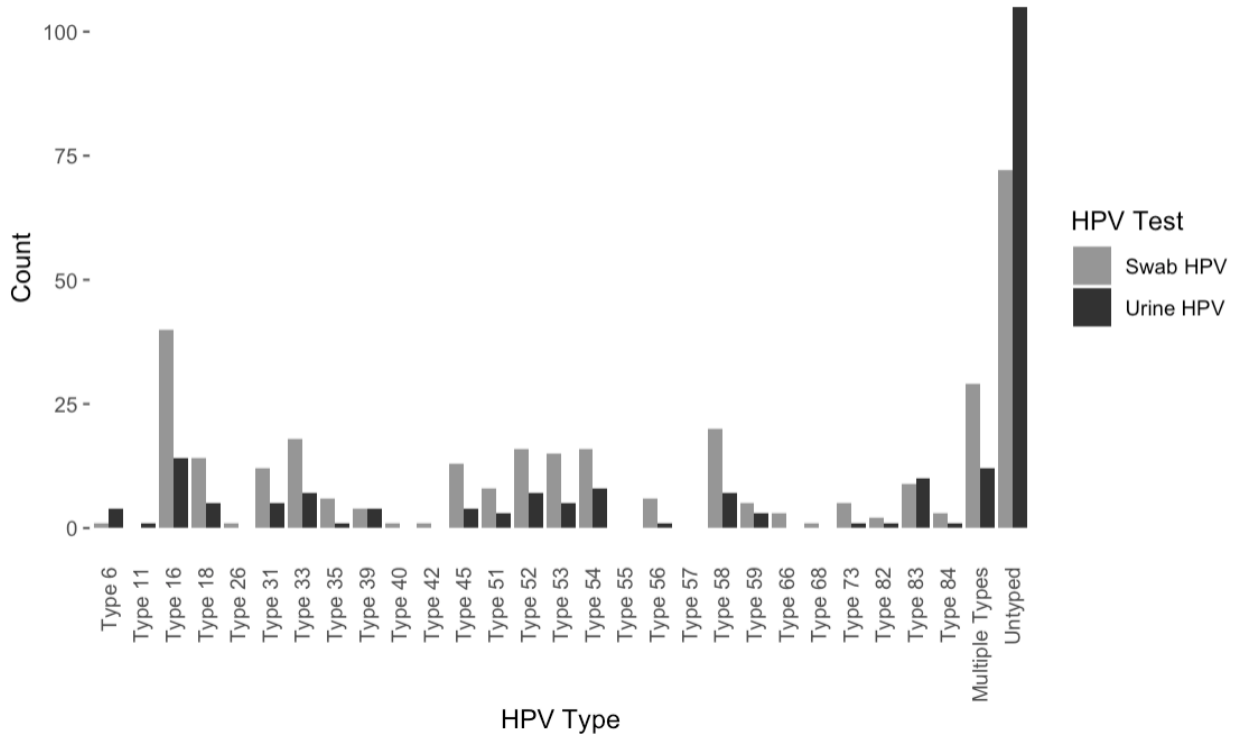


Table 2. Sensitivity, Specificity, PPV, and NPV of Urine HPV Samples Compared to Clinical-Swab HPV Samples for All HPV Types, Any HR HPV Type, and The Five Most Common HR HPV Types, 1998-2001 (N = 1397)

Diagnostic Test	All HPV	Any HR HPV	HPV 16	HPV 18	HPV 33	HPV 52	HPV 58
Sensitivity							
	98/248 (39.5%)	40/147 (27.2%)	11/40 (27.5%)	4/14 (28.6%)	7/18 (38.9%)	4/16 (25.0%)	4/20 (20.0%)
Specificity							
	1067/1149 (92.9%)	1235/1250 (98.8%)	1354/1357 (99.8%)	1382/1383 (99.9%)	1379/1379 (100%)	1378/1381 (99.8%)	1374/1377 (99.8%)
PPV							
	98/180 (54.4%)	40/55 (72.7%)	11/14 (78.6%)	4/5 (80.0%)	7/7 (100%)	4/7 (57.1%)	4/7 (57.1%)
NPV							
	1067/1217 (87.7%)	1235/1342 (92.0%)	1354/1383 (97.9%)	1382/1392 (99.3%)	1379/1390 (99.2%)	1378/1390 (99.1%)	1374/1390 (98.9%)

Table 3. Sensitivity, Specificity, PPV, and NPV of Urine HPV Samples Compared to Clinical-Swab HPV Samples Stratified by Age, 1998-2001 (N = 1382)

Age Group	Test	Swab +		Swab -		Sensitivity	Specificity	PPV	NPV
		TP	FN	FP	TN				
< 45									
	Urine	63	93	56	697	63/156 (40.4%)	697/753 (92.6%)	63/119 (52.9%)	697/790 (88.2%)
45+									
	Urine	33	55	24	361	33/88 (37.5%)	361/385 (93.8%)	33/57 (57.9%)	361/416 (86.8%)

[a] Breslow-Day test: $X^2 = 0.03$; p-value = 0.86

Table 4. HPV-Positive Samples According to Histology/Cytology Combined Results, 1998-2001

Combined Diagnosis	Normal	Atypical	LSIL	HSIL	ICC	Adeno	Other Cancer	Unsat	NA
Urine HPV Positive Proportions									
	116/1026 (11.3%)	6/44 (13.6%)	10/27 (37.0%)	9/38 (23.7%)	18/43 (41.9%)	1/4 (25.0%)	0/5 (0.0%)	20/207 (9.7%)	0/3 (0.0%)
Swab HPV Positive Proportions									
	134/1026 (13.1%)	8/44 (18.2%)	13/27 (48.1%)	28/38 (73.3%)	32/43 (74.4%)	3/4 (75.0%)	1/5 (20.0%)	28/207 (13.5%)	1/3 (33.3%)
Total Participants									
	1026	44	27	38	43	4	5	207	3

Table 5a. Sensitivity, Specificity, PPV, and NPV of Urine HPV Samples Compared to Histology/Cytology Results, 1998-2001 (N = 1169)

HPV Detection in Urine	Histology/Cytology Combined Results		Total
	HSIL+	LSIL/Negative	
Positive	27	132	159
Negative	54	956	1010
Total	81	1088	1169
	Sensitivity: 33.3%		
	Specificity: 87.9%		
	PPV: 16.9%		
	NPV: 94.7%		

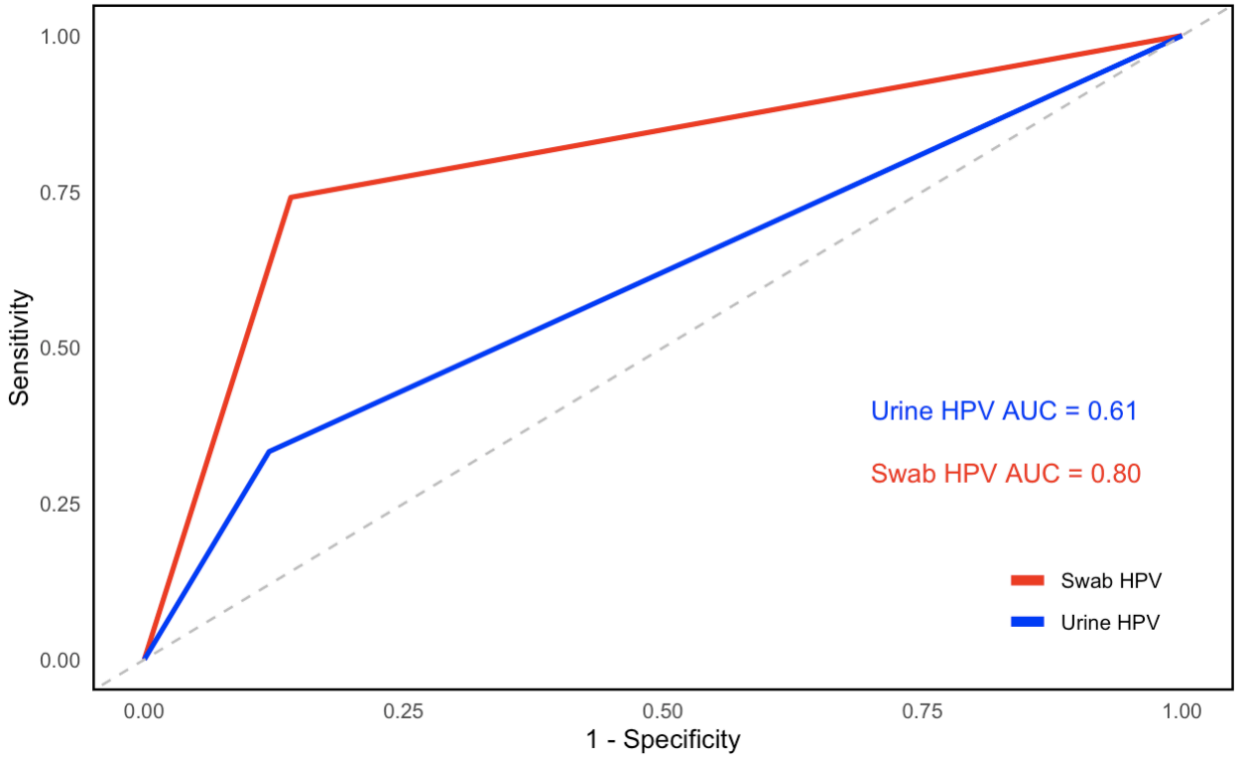
[a] Categories: Adenocarcinoma, Other Cancer, and Unsatisfactory were removed from this analysis
[b] AUC Analysis for Urine HPV: 0.61

Table 5b. Sensitivity, Specificity, PPV, and NPV of Clinical Swab HPV Samples Compared to Histology/Cytology Results, 1998-2001 (N = 1178)

HPV Detection in Swabs	Histology/Cytology Combined Results		Total
	HSIL+	LSIL/Negative	
Positive	60	155	215
Negative	21	942	963
Total	81	1097	1178
	Sensitivity: 74.1%		
	Specificity: 85.9%		
	PPV: 27.9%		
	NPV: 97.8%		

[a] Categories: Adenocarcinoma, Other Cancer, and Unsatisfactory were removed from this analysis
[b] AUC Analysis for Swab HPV: 0.80

Figure 2. ROC Curves for Urine and Swab HPV Tests in Comparison to Histology/Cytology Results (detection of HSIL+), 1998 - 2001



Legend:
AUC = Area under the Curve
HSIL+: HSIL or ICC detected by histology or cytology
LSIL/Negative: Negative, Atypical, or CIN-1 detected by histology or cytology

Appendix

Table 6. HPV-Positive Samples According to Histology Results (N = 280), 1998-2001

Histology Results	Negative	Atypical	CIN-1	CIN-2/3	CIS	AIS	ICC	Adeno	Other Cancer	Unsat	NA
Urine HPV Positive Proportions											
	24/166 (14.5%)	1/4 (25.0%)	6/20 (30.0%)	4/13 (30.8%)	4/21 (19.0%)	1/1 (100.0%)	16/41 (39.0%)	1/4 (25.0%)	0/5 (0.0%)	1/5 (20.0%)	122/1117 (10.9%)
Swab HPV Positive Proportions											
	50/166 (30.1%)	1/4 (25.0%)	9/20 (45.0%)	6/13 (46.2%)	19/21 (90.5%)	1/1 (100.0%)	30/41 (73.2%)	3/4 (75.0%)	1/5 (20.0%)	3/5 (60.0%)	125/1117 (11.2%)
Total Participants											
	166	4	20	13	21	1	41	4	5	5	1117