Comparison of Two Tests for Detecting Carcinogenic HPV in Women with Papanicolaou Smear Reports of ASCUS and LSIL

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BACKGROUND. The detection of cancer-associated types of human papillomavirus (HPV) in cervical specimens predicts the presence and future development of cervical intraepithelial neoplasia (CIN). The purposes of this study were (1) to determine the efficacy of a second-generation assay by hybrid capture (HC II) to detect carcinogenic HPV from residual cervical cells of a liquid-based cervical cytologic specimen, and (2) to compare the performance of this second-generation test with the first-generation hybrid capture (HCT) HPV test of material from direct cervical sampling to detect CIN in women with atypical squamous cells of undetermined significance (ASCUS) and low-grade squamous intraepithelial lesion (LSIL) Papanicolaou (Pap) smear reports.

METHODS. Women with a recent Pap smear report of ASCUS or LSIL had a sampling of the cervix using either an Ayre's spatula and cytobrush or an Accellon device sampling for liquid-based cytologic system HC II HPV testing, followed by a Dacron swab sampling of the cervix for standard HCT HPV testing of the paired specimens. All women received colposcopy examinations including cervical biopsy and endocervical curettage, when indicated, to determine criterion standards for comparison.

RESULTS. Paired swabs and liquid-based cervical specimens from 242 women were available for testing by standard HCT and the newer HC II HPV DNA assays. The sensitivity, specificity, and positive and negative predictive values for detecting CIN grade 2 or 3 (CIN 2/3) were 61.9%, 57.0%, 12.0%, and 94.0%, respectively, for the HCT test, and 90.5%, 29.4%, 10.9%, and 97.0%, respectively, for the liquid-based cytology HC II assay. When only women with an initial ASCUS Pap smear report were considered, the HC II test results were 88.9%, 40.3%, 9.1%, and 98.2%, respectively.

CONCLUSIONS. Testing for lower genital tract carcinogenic HPV DNA using a cervical cytology liquid transport media residual sample is clinically feasible. The new HC II microplate HPV test achieved a greater test sensitivity for detecting carcinogenic HPV and correspondingly of CIN 2/3 compared with the currently available first-generation HC HPV test. Use of a liquid-based cervical cytology system combined with intermediate triage by HC II testing of residual cells for carcinogenic HPV alone may help to efficiently identify CIN 2/3 in women who have a prior screening Pap smear report of ASCUS.

KEY WORDS. Papanicolaou; DNA probes, HPV; colposcopy; cervical dysplasia. *(J Fam Pract 1998; 46:136-141)*

Laboratory tests for human papillomavirus (HPV) have evolved extensively during the past two decades. Prior skepticism of HPV testing was based on less accurate, early generations of HPV assays (filter in situ hybridization and dot blot) and a minimal understanding of the natural history of HPV.[1] The convincing epidemiological proof that high-risk HPV types are key cervical carcinogens and the principal cause of cervical cancer worldwide has shifted current thinking about the lack of clinical utility of HPV testing.[2,3] Contemporary, commercially available, hybrid capture tube-based (HCT) HPV deoxyribonucleic acid (DNA) assays have replaced the older assays because of their ability to better detect and quantify the amount of carcinogenic HPV DNA present.[4-8] Polymerase-chain reaction HPV assays are also quite sensitive but are not currently FDA-approved for routine testing.[9] A refined version of the HCT assay, known as Hybrid Capture II (HC II), is based on a microplate format that simplifies laboratory work for detecting carcinogenic HPV types. The HC II has been modified to improve test analytical sensitivity and the probe mix has been expanded to include four additional cancer-associated HPV types 39, 58, 59, and 68.

Clinicians should, under certain circumstances, consider testing women for carcinogenic HPV.[5,10] Approximately 25% of women who have atypical squamous cells of undetermined significance

Submitted, revised, September 22, 1997.
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(ASCUS) Papanicolaou (Pap) smear reports will have cervical intraepithelial neoplasia (CIN) documented by colposcopically directed biopsy.[4] Because the majority of these women with Pap smear reports of ASCUS do not harbor CIN, serial monitoring with Pap smears to detect more severe subsequent cytologic abnormalities may be a reasonable management option instead of subjecting all women to an immediate colposcopy examination.

Clinical use of less complex, less invasive, or less expensive tests that can reliably predict which patients may truly have disease, as an alternative form of evaluation, has been termed "intermediate triage." Intermediate triage by HPV DNA testing, potentially complementary to the Pap smear and perhaps simpler than evaluation by colposcopy, has been advocated as an alternative management approach.[11]

Several researchers have demonstrated the clinical efficacy of intermediate triage of women with ASCUS and low-grade squamous intraepithelial lesions (LSIL) Pap smear reports using first-generation HCT HPV testing.[4-6,8] These studies evaluated intermediate triage with an HCT HPV test using cervical cells obtained by a direct sampling method (specimen brush or swab placed directly in a transport tube for only HPV testing). Women with a positive carcinogenic HPV test result are more likely to have a colposcopically apparent high-grade (CIN 2/3) lesion or, in rare circumstances, a cancer of the cervix. Women who have positive test results for HPV and do not have colposcopic evidence of a high-grade lesion at initial examination appear to be at increased risk for developing a significant cervical lesion during the next several years.[12]

Currently, if women are discovered to have a mildly abnormal Pap smear and "intermediate triage" by HPV testing is preferred management, then women must return to the clinic to provide another cervical specimen. Pap smears have been obtained historically by a direct transfer of cervical cells from various sampling devices to a glass slide for microscopic interpretation. Recently a new approach to cervical cytologic sampling has been introduced (ThinPrep, Cytyc Co, Boxborough, Mass), wherein the cytologic collection device is immersed directly into liquid transport media (PreservCyt, Cytyc Co). The cervical cells are collected onto a special filter to form a uniform monolayer of cells and then transferred to a glass slide with a special sample processor.[13] This Pap smear preparation does not use all of the available cervical cells in solution and residual cervical cells remaining in the liquid transport media can be used for other diagnostic purposes. Such availability of "leftover" cells could be clinically helpful when further patient triage or rapid testing is necessary following a Pap smear report indicating mildly abnormal changes. Provided a screening Pap smear was collected using the ThinPrep system, residual cells from the transport liquid could be tested for HPV DNA or lower genital tract pathogens. This intermediate triage approach would obviate the need for additional patient visits for HPV or sexually transmitted disease testing, perhaps resulting in reduced overall screening system cost.

The purposes of this study were (1) to determine the efficacy of a second-generation (HC II) HPV DNA test to detect carcinogenic HPV from residual cells of a liquid-based cervical cytologic specimen, and (2) to compare the performance of the HC II test with the standard HCT HPV test from a direct cervical swab sampling to detect cervical intraepithelial neoplasia (CIN) in women with Pap smear reports of ASCUS and LSIL.

METHODS

SUBJECTS

After obtaining institutional review board-approved informed consent, women 18 years of age or older were enrolled at six colposcopy clinics: the Family Medicine Center, Medical College of Georgia, Augusta, Ga; University Health Center, University of Massachusetts, Amherst, Mass; Student Health Center, Kansas University, Lawrence, Kan; Planned Parenthood of Westchester, White Plains, NY; Health Insurance Plan of New York, NY; and Columbia Prebyterian Medical Center, NY. The inclusion criteria were women with a recent Pap smear report indicating ASCUS or LSIL. Exclusion criteria included current pregnancy, women with previously diagnosed immunosuppression, a cytologic diagnosis of high-grade squamous intraepithelial lesion (HSIL) or cervical cancer within the past year, previous colposcopy or treatment of cervical neoplasia within the past year, or gynecologic conditions that precluded further cervical evaluation.

EQUIPMENT AND MATERIALS

A Dacron swab and transport tube containing specimen transport media (STM) (Digene Corporation,

Silver Spring, Md) were used to collect and transport cervical specimens for HCT HPV testing (Digene Corporation). A cytobrush (Medscand, Hollywood, Fla) and Ayre spatula or an Accellon device (Medscand) were used to collect a cervical specimen for traditional Pap smear analysis. After transferring cells to the glass slide, the cytologic collection devices were immersed in PreservCyt solution (Cytyc, Boxborough, Mass) for transport to the laboratory. HC II HPV testing was performed according to manufacturer's instructions using residual cells obtained from the PreservCyt solution following centrifugation. Test results were calculated based on the HCT (10 pg/mL) and HC II (0.2 pg/mL) positive calibrators. Positive results were recorded when carcinogenic HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, or 68 for HC II and 16, 18, 31, 33, 35, 45, 51, 52, or 56 for HCT were detected or indicated by the relative light unit reading exceeding the mean positive calibrator value (≥1). HPV testing was performed blinded at two laboratory sites.

Study Design

A Pap smear was collected from women with a recent ASCUS or LSIL Pap smear report using an Ayre's spatula and cytobrush or an Accellon collection device. The cytologic collection devices were smeared across a glass slide for conventional Pap smear testing and then immersed in the liquid-based cytologic system transport preservative. A Dacron swab was then used to sample the ectocervix and endocervical canal for HPV before being placed into a tube containing specimen transport media (STM). Residual cells from the liquid-based cytologic specimen and cells in the STM tube were then tested for carcinogenic HPV using the HC II and HCT HPV assays, respectively. Colposcopy was performed on all women as previously reported.[14] Cervical biopsies and endocervical curettage were performed when indicated. Following preparation, these pathology specimens were interpreted in a blinded fashion by one of the authors (T.C.W.).

Statistical Analysis

Sensitivity and specificity were calculated for the HCT and HC II HPV tests, using the results of colposcopically directed biopsy histology as the criterion standard. Two neoplasia thresholds were considered separately to be positive outcomes, and sensitivity, specificity, and predictive values were calculated for each. First, CIN 2/3 results on biopsy were considered to be positive, and CIN 1 and results within normal limits were considered to be negative. Second, all grades of CIN were considered to be positive, and results within normal limits were considered to be negative. Confidence intervals for sensitivity, specificity, and predictive values of positive and of negative tests were calculated, based on the F-distribution. Comparisons of sensitivity and specificity between the different diagnostic tests were made using McNemar's χ^2 statistic.

RESULTS

Paired conventional and liquid-based cervical cytologic system specimens from 242 subjects were available for HC HPV testing. The patient demographics of this cohort of young women with prior Pap smear reports of ASCUS and LSIL are reported in a companion paper in this issue of the *Journal*.[4] Of the 242 women, 21 had histologically confirmed CIN 2/3 and 92 women had CIN 1, 2, or 3. There were no cases of cervical cancer detected. The HCT results are part of a larger data set reported on pages 125-135.[4]

The results of the HCT HPV assay with swabs and the liquid-based cytologic HC II HPV assay to detect women with carcinogenic HPV and CIN 2/3 are presented in Table 1. The HC II results at a positive test threshold of 0.2 pg/mL were superior to results from the HCT assay at a 10-pg/mL threshold. Of note, 90.5% (19/21) of women with CIN 2/3 were detected by HC II testing for carcinogenic HPV from liquid-based cytology residual cells. The HCT DNA test was positive for only 61.9% (13/21) of these women with CIN 2/3. The negative predictive values were 94% for the HCT assay and 97% for the HC II assay. However, the positive predictive values were low and similar for both assays.

The ability of the same HPV assays used as intermediate triage tests to detect women with all levels of CIN was also examined (Table 1). In general, HPV test positive predictive values were much greater and negative predictive values were slightly less than found when restricting detection to women with CIN 2/3. Sensitivity and specificity were otherwise similar whether a CIN 2/3 or inclusive CIN detection criteria were considered.

Because the majority of women with LSIL Pap smear reports have carcinogenic HPV,[4] the utility of

TABLE 1

Standard Hybrid Capture (HCT) HPV Assay vs Hybrid Capture II (HC II) HPV Assay for Carcinogenic HPV Types to Detect Cervical Intraepithelial Neoplasia (CIN) 2/3 and All CIN in Women with ASCUS or LSIL Pap Smear Reports (N=242)

Assay	Sensitivity		Specificity		PPV		NPV	
	% (95%CI)	N	% (95%CI)	N	% (95%CI)	N	% (95%CI)	N
HCT[a]								
Detection of CIN 2/3	61.9 (38.4, 81.9)	13/21	57.0 (50.2, 63.6)	126/221	12.0 (6.6, 19.7)	13/108	94.0 (88.6, 97.4)	126/134
Detection of CIN	62.0 (51.2, 71.9)	57/92	66.0 (57.8, 73.5)	99/150	52.8 (42.9, 62.5)	57/108	73.9 (65.6, 81.1)	99/134
Liquid-based cytology HC II[b]								
Detection of CIN 2/3	90.5 (69.6, 98.8)	19/21	29.4 (23.5, 35.9)	65/221	10.9 (6.7, 16.4)	19/175	97.0 (89.6, 99.6)	65/67
P value[c]	.014		.001					
Detection of CIN	85.9 (77.0, 92.2)	79/92	36.0 (28.3, 44.2)	54/150	45.1 (37.6, 52.8)	79/175	80.6 (69.1, 89.2)	54/67
P value	.001		.001					

[a] Hybrid Capture tube-based HPV DNA test of a direct swab obtained cervical specimen transferred to a tube of specimen transport media.[2]
[b] Hybrid Capture II Microplate HPV DNA test of residual cells from a liquid-based cervical cytology collection system.
[c] Comparison with HCT by McNemar's test.
ASCUS denotes atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; PPV, positive predictive value; NPV, negative predictive value.

intermediate triage by HPV testing for these women should be considered questionable. Therefore, when only women with an initial Pap smear report of ASCUS were considered, the HC II test sensitivities were considerably better than the test sensitivities reported for the HCT test (Table 2). While the test specificities were better for the HCT test, there was little difference between the tests in regard to positive and negative predictive values. For comparative purposes, the results of the HCT and HC II HPV tests for women with LSIL are presented in Table 3.

DISCUSSION

The findings of our study indicate that testing for lower genital tract carcinogenic HPV DNA by HC II using liquid transport media cervical cytology residual specimens is better than testing with the first-generation HCT HPV test of a direct swab sampling of the cervix. The clinical implications of testing residual cells from a liquid-based Pap smear for carcinogenic HPV are profound. If a liquid-based Pap smear were to be used initially for all women, or simply women considered to be at high risk for cervical neoplasia, then only women determined to have an abnormal Pap smear report of ASCUS could have rapid testing for carcinogenic HPV without having to return to the clinic for an additional cervical specimen collection. Such an intermediate triage strategy would save further expenses of clinician time, patient inconvenience, tracking and recall effort, and transportation costs, provided the liquid-based cytology system is not significantly more expensive than the conventional slide-based Pap smear method. Women identified as having a carcinogenic HPV, in addition to a mildly abnormal Pap smear, would then be triaged immediately for a colposcopy examination. The remaining women found to have non–cancer-associated HPV types or no HPV, and thus considered to be at low risk for harboring a significant cervical neoplasia, could then be monitored by less expensive serial cervical cytology. The ability to test residual Pap smear cells for other sexually transmitted pathogens and neoplasia-related genes, RNAs, or proteins may also be meaningful in the future.

Our results may underestimate the true potential of liquid-based cervical cytology combined with intermediate triage by HPV testing for several reasons. First, a conventional glass slide Pap smear was universally prepared prior to immersion of the cytologic collection devices into the liquid cytology transport fluid. Thus, fewer cervical cells might have been available for liquid-based HPV testing, since a cytologic transfer to slide was initially performed. Therefore, the liquid-based HPV test performance

TABLE 2

Hybrid Capture (HCT) HPV Assay vs Hybrid Capture II (HC II) HPV Assay for Carcinogenic HPV Types to Detect Cervical Intraepithelial Neoplasia (CIN) 2/3 and All CIN in Women with ASCUS Pap Smear Reports (n=143)

Assay	Sensitivity		Specificity		PPV		NPV	
	% (95%CI)	N	% (95%CI)	N	% (95%CI)	N	% (95%CI)	N
HCT[a]								
Detection of CIN 2/3	55.6 (21.2, 86.3)	5/9	67.2 (58.5, 75.0)	90/134	10.2 (3.4, 22.2)	5/49	95.7 (89.5, 98.8)	90/94
Detection of CIN	48.7 (32.4, 65.2)	19/39	71.2 (61.4, 79.6)	74/104	38.8 (25.2, 53.8)	19/49	78.7 (69.1, 86.5)	74/94
Liquid-based cytology HC II[b]								
Detection of CIN 2/3	88.9 (51.8, 99.7)	8/9	40.3 (31.9, 49.1)	54/134	9.1 (4.0, 17.1)	8/88	98.2 (90.3, 99.9)	54/55
P value[c]	.083		.001					
Detection of CIN	79.5 (63.5, 90.7)	31/39	45.2 (35.4, 55.3)	47/104	35.2 (25.3, 46.1)	31/88	85.5 (73.3, 93.5)	47/55
P value	.001		.001					

[a] Hybrid Capture tube-based HPV DNA test of a direct swab obtained cervical specimen transferred to a tube of specimen transport media.[2]
[b] Hybrid Capture II Microplate HPV DNA test of residual cells from a liquid-based cervical cytology collection system.
[c] Comparison with HCT by McNemar's test.
ASCUS denotes aypical squamous cells of undetermined significance; PPV, positive predictive value; NPV, negative predictive value.

might have detected more cases of CIN 2/3 if more cervical cells had been collected into the vial. However, a more cellular sample may have increased the rate of HPV DNA positivity in the absence of CIN 2/3. A second factor that might affect the applicability of our results to those that would be obtained during routine screening is that all samples were obtained at the time of colposcopy in women known to have an abnormal Pap smear. The performance of both HPV DNA tests might be different if samples obtained at the time of initial Pap smear screening were analyzed.

We have demonstrated that the HC II HPV test achieved a greater sensitivity for detecting carcinogenic HPV and subsequently CIN 2/3 compared with the currently available HCT HPV test.[4] Our findings have essentially shown that the liquid-based cytologic media HC II HPV test, as an intermediate triage test for women considered to be at increased risk because of a prior ASCUS or LSIL Pap smear report, identified greater than 90% of women who harbored a high-grade cervical lesion. Although the increased test sensitivity was obtained at the expense of a reduced test specificity, proper identification of all women with high-grade cervical neoplasia, and thus a greater potential for developing cervical cancer, is worthwhile. The HC II HPV test performed well when only women with initial ASCUS Pap smear reports were considered. The utility of intermediate triage by HPV testing for women with initial LSIL Pap smears is suspect because the majority of these women harbor carcinogenic HPV.[4] The HC II test is approximately 50-fold more sensitive than the HCT test and is able to detect as low as 1000 HPV genomes per assay. Intermediate triage testing using the liquid-based cytology system and the HC II HPV test appears to be a potentially robust strategy for women with previous Pap smear reports of ASCUS.

Ferenczy et al[15] have previously reported on the use of the HCT HPV test from a liquid-based cytologic media for women with previous abnormal Pap smear reports. The sensitivity, specificity, and positive and negative predictive values of the HPV test for detecting women with CIN 2/3 were 76.6%, 63.7%, 36.4%, and 91.0%, respectively. While our test specificity and positive predictive value were lower, our reported test sensitivity (90.5%) and negative predictive value (97.0%) were greater using the more sensitive HC II HPV test.

In our study of women with prior ASCUS or LSIL Pap smear reports, we assumed that a liquid-based Pap smear collected within several months of the initial abnormal smear would reflect the presence of CIN 2/3 equally as well as if it had been the initial method of Pap smear sampling. As a cautionary note, we have not proved that using an intermediate

TABLE 3

Hybrid Capture (HCT) HPV Assay vs Hybrid Capture II (HC II) HPV Assay for Carcinogenic HPV Types to Detect Cervical Intraepithelial Neoplasia (CIN) 2/3 and All CIN in Women with LSIL Pap Smear Reports (n=99)

Assay	Sensitivity		Specificity		PPV		NPV	
	% (95%CI)	N	% (95%CI)	N	% (95%CI)	N	% (95%CI)	N
HCT[a]								
Detection of CIN 2/3	66.7 (34.9, 90.1)	8/12	41.4 (30.9, 52.4)	36/89	13.6 (6.0, 25.0)	8/59	90.0 (76.3, 97.2)	36/40
Detection of CIN	71.7 (57.7, 83.2)	38/53	54.3 (39.0, 69.1)	25/46	64.4 (50.9, 76.4)	38/59	62.5 (45.8, 77.3)	25/40
Liquid-based cytology HC II[b]								
Detection of CIN 2/3	91.7 (61.5, 99.8)	11/12	12.6 (6.5, 21.5)	11/87	12.6 (6.5, 21.5)	11/87	91.7 (61.5, 99.8)	11/12
P value[c]	.083		.001					
Detection of CIN	90.6 (79.3, 96.9)	48/53	15.2 (6.3, 28.9)	7/46	55.2 (44.1, 65.9)	48/87	58.3 (27.7, 84.8)	7/12
P value	.008		.001					

[a] Hybrid Capture tube-based HPV DNA test of a direct swab obtained cervical specimen transferred to a tube of specimen transport media.
[b] Hybrid Capture II Microplate HPV DNA test of residual cells from a liquid-based cervical cytology collection system.
[c] Comparison with HCT by McNemar's test.
LSIL denotes low-grade squamous intraepithelial lesion; PPV, positive predictive value; NFV, negative predictive value.

triage HPV test is as effective or more beneficial than the current practices of repeating the Pap smear or evaluating with colposcopy when women have ASCUS or LSIL Pap smear reports. Larger prospective trials are necessary to examine the potential utility of liquid-based cervical cytology used for initial screening of cervical neoplasia followed by intermediate HPV triage tests from residual cells, when indicated. Cost-effectiveness analyses would also be helpful to determine the overall utility of liquid-based cytology and subsequent HPV triage testing as a practical cervical neoplasia screening system.

ACKNOWLEDGMENTS

Financial support for this study was provided in part by a grant (22317) from The Robert Wood Johnson Foundation Generalist Physician Faculty Scholars Program. Some HPV DNA tests and supplies were provided at no cost by Digene Corporation, Silver Spring, Md, and Thin Prep/PreservCyt kits were provided by Cytyc Corporation, Boxborough, Mass.

Special thanks to Alice Randolph for manuscript preparation assistance. We also appreciate the clinical assistance of William Buck, MD, Lawrence, Kansas; Richard Rubin, MD, Amherst, Mass; Larry Kramer, MD, New York, NY, and Lynn Borgatta, MD, White Plains, NY.

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