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Very Low Human Papillomavirus DNA Prevalence in Mature Women With Negative Computer-Imaged Liquid-Based Pap Tests

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BACKGROUND. The prevalence of high-risk Human Papillomavirus DNA (hrHPV DNA) in women with negative Papanicolaou (Pap) test results provides a measure of residual risk for cervical neoplasia after cytology screening. The purpose of this study was to document the prevalence of hrHPV DNA in several thousand women ages $\geq$30 years with negative ThinPrep Imaging System (TIS)-imaged Pap test results in a large academic hospital cytology laboratory.

METHODS. All cytology-negative TIS-imaged ThinPrep Pap tests (TPPT) with hrHPV DNA tests that were performed by the United States Food and Drug Administration (FDA)-approved Hybrid Capture 2 (HC2) method from May 1, 2005 to November 20, 2006 were identified and reviewed. Imaged-negative Pap test slides associated with a positive hrHPV DNA test result were rescreened manually. Variation in hrHPV DNA prevalence was assessed for different age and ethnic groups.

RESULTS. Of 8070 imaged cytology-negative TPPT from women ages 11 to 90 years, hrHPV DNA test results were also available. Among 7426 women ages $\geq$30 years with a cytology-negative, TIS-imaged, Pap test, a significant age-associated decline in hrHPV DNA prevalence was noted, 3.4% in 3050 women ages 30–45 years, 2.4% in 7426 women ages 30–90 years, and 1.8% in 5491 women ages 40–90 years. The hrHPV DNA-positive rate was 2.3% in 6012 imaged cytology-negative white women and 4.1% in 739 imaged cytology-negative black women.

CONCLUSIONS. Very low HC2 hrHPV DNA rates in 7426 women ages $\geq$30 years with cytology-negative, TIS-imaged, ThinPrep, Pap tests were similar to recently published data from 1 other academic center and lower than rates reported in previous studies on cytology-negative North American or European women screened manually with conventional or liquid-based Pap tests. These data may impact assessments of how best to combine cytology and HPV testing. ***Cancer (Cancer Cytopathol)*** **2007;111:292–7.** *© 2007 American Cancer Society.*

KEYWORDS: Human Papillomavirus, Hybrid Capture 2 test, liquid-based cytology, computer-assisted screening, Papanicolaou (Pap) test, ThinPrep Pap test, ThinPrep imaging system.

In 2003, the US Food and Drug Administration (FDA) approved adjunctive high-risk Human Papillomavirus DNA (hrHPV DNA) testing with cytology screening for women ages $\geq$30 years.[1] Since then, several clinical trials[2] and modeling studies[3–8] have attempted to further evaluate various cervical cancer screening formulations by using different combinations of conventional and liquid-based cervical cytology (LBC) and hrHPV DNA testing. One very recent modeling study by US Army clinical investigators concluded that the most cost-effective combination screening strategy was LBC every 2

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years with limited hrHPV DNA testing only after a cytological finding of atypical squamous cells of undetermined significance (ASCUS).[3] These investigators concluded that routine cytology and hrHPV DNA cotesting, although predicted in their model to be the most successful strategy for preventing cervical cancer deaths, was questionably cost effective. No published studies, however, have looked at the impact of location-guided computer-assisted screening of LBC, approved by the FDA in 2003 and now widely used in the US with the ThinPrep-Imaging System (TIS),[9] on evaluations of different possible screening formulations that use both cytology and hrHPV DNA testing. Available studies indicate that this technology further enhances[10,11] the improved ability of LBC[12,13] to reliably detect significant precancerous and neoplastic cervical lesions. Because hrHPV DNA provides an objective measure of residual risk for cervical neoplasia after cytology screening, we have examined the prevalence of hrHPV DNA in women with negative TIS-imaged cytology results.

MATERIALS AND METHODS

After obtaining institutional review board approval at the University of Pittsburgh Medical Center (UPMC), a retrospective study was initiated. All Papanicolaou (Pap) tests between May 2005 and November 20, 2006 (165,874 tests) were identified in a CoPath computer database (Cerner, Kansas City, Mo). Beginning in May 2005, all hrHPV DNA test results were entered routinely into the CoPath anatomic pathology database. During this period there were 159,975 (96.5%) ThinPrep Pap tests (TPPT)[14] (Cytyc, Marlborough, Mass) and 5899 (3.5%) conventional Pap smears. The current study focused on all patients with TPPT reported as negative for intraepithelial lesion or malignancy who also were tested for hrHPV DNA. All specimens were processed and evaluated in the pathology laboratory at Magee-Womens Hospital of University of Pittsburgh Medical Center and reported with current Bethesda System 2001 terminology.

TPPT were prepared according to manufacturer's specifications from PreservCyt (Cytyc, Marlborough, Mass) samples by using an automated processor (ThinPrep 3000). Staining of slides was performed on a Sakura Tissue Tek Automated Slide Stainer (Somagen Diagnostics, Edmonton, Alberta, Canada) according to an FDA-approved manufacturer's protocol. Location-guided computer-assisted screening of TPPT slides was accomplished by using the ThinPrep Imaging System (TIS). The TIS performed analysis of batches of up to 250 ThinPrep Pap test slides with specialized imaging software. For each slide, the locations of 22 microscopic fields that contained cells or cell clusters of interest were recorded. The imaged TPPT slides were placed on cytotechnologist review scopes, and the cytotechnologists reviewed the 22 fields in geographic order. If the cytotechnologists found no abnormalities on those 22 fields, the cytotechnologist could sign out the case as negative. In all cases in which any of the 22 fields contained any abnormality, reactive or reparative cellular changes, or microorganisms, the cytotechnologists manually rescreened the entire TPPT slide. All cases interpreted by cytotechnologists as abnormal or as showing reactive or reparative changes were referred to a pathologist for review.

hrHPV DNA testing was ordered by clinicians according to several ordering options as follows: reflex testing triggered by indeterminate abnormal atypical squamous cell (ASC) Pap test results, routine cotesting with Pap testing in women ages $\geq$30 years (DNA with Pap), and hrHPV DNA cotesting regardless of age or Pap test result (HPV regardless). If hrHPV DNA was positive in cytologically negative Pap tests, the Pap test slides were routinely manually rescreened by the screening cytotechnologist, referred for further manual rescreening by a quality-assurance cytotechnologist, and then, in addition, reviewed by a pathologist.

hrHPV DNA detection was performed by the commercially available FDA-approved Hybrid Capture II (HC2) System[15] (Digene Corp., Gaithersburg, Md), which tests for high-risk and intermediate-risk HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. This enzyme-linked immunosorbent assay is based on a sandwich-capture molecular hybridization technique followed by a nonradioactive alkaline phosphatase reaction with chemoluminescence in microplates. Cases were categorized as either HC2 positive or HC2 negative based on a threshold of 1 pg/mL HPV DNA. For purposes of this study, all cytologically negative TPPT slides that tested positive for hrHPV DNA were further reviewed independently by 2 cytopathologists. If questionable abnormalities were detected by either cytopathologist, the slides were reviewed for adjudication by a third senior cytopathologist.

Statistical Analysis

Confidence intervals for the positive rates of hrHPV DNA were obtained. The positive rate of hrHPV DNA for each age group was compared with that of the reference group. The *P*-values were obtained for the null hypothesis, which was that a positive rate of hrHPV DNA for each age group equals that of the reference group. Logistic regression[16] was also used to predict the rate change by using the age group as the predictor. The predictor was coded as 0 (ages 11–

TABLE 1
Age-Specific hrHPV Prevalence Among Women With Imaged Negative TPPT (10-Year Intervals)

Age groups, y	HPV tested No.	HPV+ No. (%)	95% CI	*P*
11–20	131	11 (8.4)	3.7–13.2	Reference
21–29	513	43 (8.4)	5.1–9.0	.597
30–40	1935	77 (4.0)	3.2–5.0	.082
41–50	2354	43 (1.8)	1.3–2.4	.007
51–60	2125	36 (1.7)	1.2–2.2	.006
61–70	749	13 (1.7)	0.8–2.7	.007
71–80	217	5 (2.3)	0.3–4.3	.020
81–90	46	2 (4.3)	0.0–10.2	.294
Total	8070	230 (2.9)	2.5–3.2	

hrHPV indicates high-risk human papillomavirus; TPPT, ThinPrep Pap test.
P value was calculated by comparing each group with reference group, respectively.

20 years), 1 (ages 21–30 years), ..., 7 (ages 81–90 years) for 10-year interval data.

RESULTS

From May 1, 2005 to November 20, 2006, 165,874 Pap tests, including 159,975 TPPT and 5899 conventional Pap smears, were reviewed at Magee-Womens Hospital of University of Pittsburgh Medical Center. TPPT were routinely imaged with the TIS. hrHPV DNA testing was ordered and completed in 8074 patients who also had negative TPPT results, including cases with reparative or reactive cellular changes. Four cases were excluded in this study because we retrospectively interpreted them as having cytologic abnormalities on subsequent reviews.

A total of 8070 women with cytologically negative TPPT had hrHPV DNA testing completed. The age of women with cytologically negative TPPT and hrHPV DNA testing ranged from 11 to 90 years. The age-related hrHPV DNA prevalence was analyzed in10-year intervals with their 95% CI; *P* values are listed in Table 1. Cytology-negative women who tested positive for hrHPV DNA were significantly more likely to be younger, with peak infection rate occurring in women younger than 30 years (Table 2), and there was a clear decline in the hrHPV DNA prevalence in older age groups. The hrHPV DNA rate in 1935 women ages 30–40 years was 4.0% and 1.8% in 5491 women ages ≥41 years. In 3050 women ages 30–45 years, the age group surveyed in 1 previous study,[17] the hrHPV DNA rate was 3.4% (not shown in Table 1).

Age-specific hrHPV DNA prevalence in women with cytologically negative TPPT was analyzed by logistic regression in 10-year intervals. The proportion, p_x, of positive cases was predicted by age x through the formula

$$p_x = \exp(a + bx) \div \{1 + \exp(a + bx)\}.$$

At 10-year intervals, the results were $a = -2.411$ with a standard error of 0.152 and $b = -0.397$ with a standard error of 0.054. Both a and b were highly significant, indicating that hrHPV DNA prevalence was strongly correlated with age.

TABLE 2
Comparison of hrHPV DNA-Positive Rates Between Women Ages ≥30 Years and Younger Women with Imaged Negative TPPT

Age groups, y	HPV tested No.	HPV+ No. (%)	95% CI	*P*
<30	644	54 (8.4)	6.3–10.5	1.7×10^{-7}
≥30	7426	176 (2.4)	2.0–2.8	

hrHPV indicates high-risk human papillomavirus; TPPT, ThinPrep Pap test.

Further analysis was carried out on hrHPV DNA prevalence in TIS-imaged cytologically negative TPPT; hrHPV DNA prevalence was highest (8.4%) in women ages 11–29 years (Table 2) and decreased to 1.8% in women older than 40 years. hrHPV DNA prevalence was statistically significantly higher in women younger than 30 years compared with women ages 30 years and older (Table 2). The difference in hrHPV DNA prevalence between women ages 11 to 20 years and women ages 21 to 29 years was not statistically significant ($P = .597$). A statistically significant decline in hrHPV DNA prevalence from 7% in women 21–29 years of age to 4.1% in women in 30–40 years of age (comparison of hrHPV DNA prevalence between women ages 21–29 years and ages 30–40 years, $P = .007$) was observed. hrHPV DNA prevalence continued a statistically significant decline to 1.8% in women ages 41–50 years (comparison of hrHPV DNA prevalence between women ages 30–40 years and 41–50 years, $P = 3 \times 10^{-5}$). In subsequent age groups, hrHPV DNA prevalence did not significantly continue to decline and remained fairly stable in women after the age of 40 years.

The relation between hrHPV DNA prevalence and ethnicity was also analyzed in this study. Ethnic background was available in 6814 (84.4%) of 8070 cytology-negative women who had hrHPV DNA results, with the following distribution, 6012 white, 739 black, 59 Asian, 4 Hispanic, and 1256 unknown women. The percentage distribution by ethnic background was 88.2%white women, 10.9% black women, and 0.9% other. The overall hrHPV DNA-positive rate was 2.3% (95% CI, 1.9%–2.7%) in white women, and

TABLE 3
Comparison of hrHPV DNA-Positive Rates Between White and Black Women Ages ≥30 Years and Younger Women With Imaged Negative TPPT

	HPV tested No.	HPV+ No. (%)	95% CI	*P*
White women				
Age groups, y				2×10^{-4}
<30	384	26 (6.8)	4.3–9.3	
≥30	5628	113 (2.0)	1.6–2.4	
Black women				
Age groups, y				.023
<30	97	10 (10.3)	4.3–16.3	
≥30	642	20 (3.1)	1.8–4.4	

hrHPV indicates high-risk human papillomavirus; TPPT, ThinPrep Pap test.

4.1% (95% CI, 2.6%–5.5%) in black women. The difference in hrHPV DNA-positive rate between these 2 ethnic groups was statistically significant ($P = .02$). The odds ratio for hrHPV prevalence between white and black women is 0.559. For both black and white women, the hrHPV DNA rate in TIS-imaged cytology-negative women older than 30 years of age was <3.5% (Table 3).

DISCUSSION

The prevalence of hrHPV DNA detected by the FDA-approved HC2 test method in general-screening groups of North American and European women with manually screened cytologically negative conventional and LBC Pap test results has been reported to vary from 5.4% to 17.1%.[18–23] In our study, hrHPV DNA-positive rates declined significantly in women ages ≥30 years, as noted in numerous other studies.[22–25] In at least 1 other study, a very low hrHPV DNA rate of 3.9% was also reported in 1000 cytology normal women ages ≥30 years[30–45] who had been screened with TIS-imaged TPPT.[17] The current study confirms and extends those observations with a larger dataset of more than 8000 cytologically negative patients with HC2 hrHPV DNA test results after TIS location-guided computer-assisted screening of TPPT. The very low rates of hrHPV DNA also noted here in the relatively small sample (8%) of imaged cytology-negative women ages <30 years probably reflects a variety of factors, including selective testing of a relatively affluent group of low-risk young women willing to pay for testing not covered by most local insurance plans, the lower hrHPV DNA prevalence at this study site documented in the ASCUS/LSIL Triage Study For Cervical Cancer (ALTS) (unpublished data), and the efficacy of the TIS in identifying hrHPV DNA-positive cases not identified in routine manual screening. The high proportion of white women in the study population clearly impacted the very low hrHPV DNA rates detected in cytologically negative women in this study. Although hrHPV DNA prevalence varied significantly in imaged cytology-negative black and white women, very low hrHPV DNA rates were documented in both groups for women ages ≥30 years with negative TIS-imaged TPPT.

In 2003, the FDA approved the HC2 HPV DNA test for adjunctive use along with Pap testing in cervical screening of women ages 30 years and older.[1] The high rate of hrHPV DNA test results in women younger than 30 years of age was judged, at that time, to preclude broader routine application of adjunctive cotesting in younger women. A major rationale for FDA approval for women ages ≥30 years was the low risk for development of cervical intraepithelial neoplasia CIN3+ lesions in women who tested negative with both Pap testing and HC2 hrHPV DNA testing.[26] Cost-benefit analyses available at that time also suggested that the increased cost of combining HPV DNA testing with cytology could be somewhat offset by increasing the screening interval for double-negative women ages ≥30 years.[27]

In our laboratory, hrHPV DNA was detected by HC2 in only 2.4% of 7426 women older than 30 years of age with cytology negative TIS-imaged TPPT. The ability of a new cytology-based method to identify negative Pap-test slides in women with very low residual hrHPV DNA rates suggests that the cost effectiveness of adding routine hrHPV DNA cotesting to TIS-imaged Pap testing needs to be re-evaluated against a more selective strategy of reflex hrHPV DNA testing limited to patients with indeterminate (atypical) Pap test results. Bidus' US Army evaluation, for example, showed that a strategy of LBC and reflex-limited HPV testing every 2 years was clearly cost effective with an estimated incremental cost-per-life-year saved of $56,728.[3] This cost-effective strategy dominated routine hrHPV DNA and Pap cotesting at both 2-year and 3-year intervals because the significantly higher costs associated with routinely combining hrHPV DNA testing (CPT code 87621; 2007 Medicare payment $49.04) with LBC (CPT code 88142; 2007 Medicare payment $28.31) for routine primary screening. The cost disadvantage for routine primary hrHPV DNA cotesting is not significantly different when HPV testing is combined with TIS-imaged Pap screening (CPT code 88175; 2007 Medicare payment $37.01). Detailed cost-effectiveness studies that use system data are being planned in collaboration with University of Pittsburgh econo-

mists. In 1 preliminary cost-effectiveness model evaluation, the TIS was judged to be a highly cost-effective screening strategy.[28]

The likelihood of cytology-negative patients with a single, positive, HC2 hrHPV DNA test of developing highly significant (CIN3+) precancerous or malignant lesions in long-term (10-year) follow-up appears to be very low. In the Portland, Oregon, National Cancer Institute prospective risk study that used conventional Pap smears rather than LBC, the 10-year cumulative risk of developing CIN3+ lesions was 3%–6% for conventional cytology-negative HC2 hrHPV DNA-positive women.[29–32] In another more recent Danish prospective risk study that also used conventional Pap smears, the 10-year CIN3+ risk reported in cytology-negative hrHPV DNA-positive patients was somewhat higher at 13.6%–23% and was highest in older patients.[33] Given data from prospective risk studies[29–33] and the very low hrHPV DNA prevalence here in TIS-imaged, Pap-negative women ages $\geq$30 years, the long-term risk of undetected significant cervical disease in our TIS-imaged, Pap-negative patients appeared to be extremely low. Future trials will need to compare the low risk of undetected significant cervical disease after imaged screening to the risk of undetected significant cervical disease in patients with negative HC2 hrHPV DNA test results[21,34] One recent editorial, for example, argued that according to today's achievable standards, a range of 89%–95% hrHPV DNA-test sensitivity is acceptable.[35] We are now beginning a long-term follow-up study of TIS-imaged cytology negative hrHPV DNA-positive women in this large integrated health plan practice.

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