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Human Papillomavirus Infection and Cervical Cytology in Women Screened for Cervical Cancer in the United States, 2003–2005

S. Deblina Datta, MD; Laura A. Koutsky, PhD; Sylvie Ratelle, MD†; Elizabeth R. Unger, MD, PhD; Judith Shlay, MD, MSPH; Tracie McClain, MD; Beth Weaver, MD; Peter Kerndt, MD; Jonathan Zenilman, MD; Michael Hagensee, MD, PhD; Cristen J. Suhr, MPH, CHES; and Hillard Weinstock, MD, MPH

Background: Millions of women in the United States receive cervical screening in sexually transmitted disease (STD), family planning, and primary care clinical settings.

Objective: To inform current cervical screening programs.

Design: Measurement of abnormal Papanicolaou (Pap) tests and high-risk human papillomavirus (HPV) infection among demographically diverse women who received routine cervical screening from January 2003 to December 2005 in the United States.

Setting: 26 STD, family planning, and primary care clinics in 6 U.S. cities.

Patients: 9657 women age 14 to 65 years receiving routine cervical screening.

Measurements: Pap test results and high-risk HPV prevalence by Hybrid Capture 2 assay (Digene, Gaithersburg, Maryland).

Results: Among 9657 patients, overall high-risk HPV prevalence by Hybrid Capture 2 testing was 23% (95% CI, 22% to 24%). Prevalence was highest among women age 14 to 19 years (35% [CI, 32% to 38%]) and lowest among women age 50 to 65 years (6% [CI, 4% to 8%]). Prevalence by clinic type (adjusted for age and city) ranged from 26% (CI, 24% to 29%) in STD clinics to 17% (CI, 16% to 20%) in primary care clinics. Women younger than 30 years of age whose Pap test showed atypical squamous cells of undetermined significance had a high-risk HPV prevalence of 53%; women 30 years of age or older with normal Pap tests had a 9% prevalence. Values did not vary substantially by clinic type.

Limitation: Hybrid Capture 2 and Pap testing were noncentralized, and consent was required for enrollment.

Conclusion: High-risk HPV was widespread among women receiving cervical screening in the United States. Many women 30 years of age or older with normal Pap tests would need follow-up if Hybrid Capture 2 testing is added to cytology screening.

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For author affiliations, see end of text.
†Deceased.

Broadly based cervical screening programs in the United States, which are typically administered in primary or family planning medical care settings or selected sexually transmitted disease (STD) clinics, are aimed at detecting and treating cervical cytologic abnormalities. In these programs, Papanicolaou (Pap) tests are used to detect precancerous lesions early and prevent invasive cervical cancer. The programs have decreased the annual number of cervical cancer cases to approximately 11 892 and decreased deaths to 3850 in 2004 (1). Current guidelines from the U.S. Preventive Services Task Force (USPSTF) (2), American Cancer Society (ACS) (3), and American College of Obstetricians and Gynecologists (ACOG) (4) recommend that women start cervical screening with Pap tests at 21 years of age (or within 3 years of initiating sexual activity) and get screened at least every 3 years up to age 65 years (USPSTF) or 70 years (ACS); ACOG does not specify an upper age limit.

Persistent cervical infection with oncogenic, or high-risk, types of human papillomavirus (HPV) is a necessary but not sufficient causal agent of cervical cancer (5); high-risk HPV types (most commonly, type 16) have been identified in more than 99% of cases of cervical cancer (6). Cervical screening programs historically used Pap testing alone; however, high-risk HPV DNA testing with the commercially licensed Hybrid Capture 2 assay (Digene, Gaithersburg, Maryland) has been suggested for use in 2 specific scenarios in an effort to improve screening and management. The first and most common use is for triage of women whose Pap tests show atypical squamous cells of undetermined significance (ASC-US), in a strategy known as *reflex testing* (with referral of Hybrid Capture 2–positive women for colposcopy). The second and more recent recommendation is as a co-test for routine cervical screening in women age 30 years or older, regardless of Pap test results (with repeated Pap and Hybrid Capture 2 testing recommended in the event of normal Pap test results and positivity for high-risk HPV). The American Society for Colposcopy and Cervical Pathology (ASCCP) and ACOG make recommendations for reflex testing in cervical screening, and ACS, ACOG, and ASCCP

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Context

Some cervical cancer screening programs use reflex testing, performing tests for high-risk human papillomavirus (HPV) only after abnormal Papanicolaou (Pap) tests to guide colposcopy decisions. Others perform both tests in women 30 years of age or older (co-testing) and repeat testing if either result is abnormal. Lack of data limits analysis of the usefulness of different screening strategies.

Contribution

The Pap and high-risk HPV tests in 9657 women in 26 sexually transmitted disease, family planning, and primary care outpatient clinics from 2003 to 2005 showed that 23% were positive for high-risk HPV. Among women older than 30 years with normal Pap tests, 9% tested positive for high-risk HPV.

Implication

These data suggest that many women older than 30 years with normal Pap tests would require additional follow-up in programs that co-test with HPV testing and cytology.

—The Editors

have recommendations for co-testing; in contrast, the USPSTF issued an "I" statement (insufficient evidence) regarding the use of any Hybrid Capture 2 testing in cervical screening.

Recently, the ASCCP eliminated its recommendation for Hybrid Capture 2 testing in women younger than age 21 years because of the high prevalence and short duration of high-risk HPV infection in this group (7). It also changed the follow-up period for women older than age 30 years with normal Pap tests and positive Hybrid Capture 2 tests from the previously recommended 6 to 12 months to a definitive 12 months. Lack of broad-based data on Pap test results and high-risk HPV infection (as detected by Hybrid Capture 2 testing) has severely hampered appropriate policy analyses of screening guidelines and has led to differences in recommendations across policy-making bodies.

The HSS (HPV Sentinel Surveillance) project enrolled women attending 26 STD, family planning, and primary care clinics in 6 U.S. cities from January 2003 to December 2005. The HSS project was designed to measure the burden of high-risk HPV infection and abnormal Pap test results in the U.S. cervical screening population by using broad sampling and standardized protocols. The HSS project is one of the largest U.S. studies to describe the high-risk HPV prevalence in demographic groups in the diverse cervical screening population and to inform clinicians about what can be expected from using HPV testing along with Pap testing, as suggested by current guidelines.

METHODS

Study Sites and Enrollment Criteria

Investigators for the HSS project from 6 cities (Boston, Massachusetts [including 2 clinics in Fitchberg and Springfield, Massachusetts]; Baltimore, Maryland; New Orleans, Louisiana; Denver, Colorado; Seattle, Washington; and Los Angeles, California) enrolled women from 26 clinics beginning in January 2003. Clinics included 8 STD clinics, 10 family planning clinics, and 8 primary care clinics. Clinics of each type were present in each city. We standardized enrollment, data collection, and laboratory testing methods by using a common protocol.

We invited women attending the clinics to enroll if they were 18 to 65 years of age and eligible for a routine cervical screening test (minimum of 12 months since their last Pap test). One clinic in Baltimore and 1 in Denver also enrolled adolescents age 14 to 17 years, a sexually active population. We excluded women who had had hysterectomy, those with a history of treatment on the cervix during the previous 12 months, and those who were currently menstruating or pregnant. This analysis includes data on women enrolled into the HSS project between 1 January 2003 and 31 December 2005 (1 January 2003 and 31 July 2005 for the New Orleans data because of Hurricane Katrina).

Data and Specimen Collection

We collected demographic information by administering a questionnaire; race and ethnicity data were collected on the basis of the enrollee's self-report. All women who did not self-identify as white, African American, Asian, Pacific Islander, American Indian, Alaskan Native, or multiracial were included in the "unknown" category. The HSS project staff abstracted medical record data (including Pap test results) from the medical charts.

Providers collected cervical samples for Pap testing at the time of pelvic examination by using the device and method (conventional or liquid-based) in routine use at each clinic. Local cytopathologists interpreted all cytology specimens by using Bethesda 2001 guidelines (normal, ASC-US, atypical squamous cells—cannot exclude high-grade squamous intraepithelial lesions [ASC-H], low-grade squamous intraepithelial lesions [LSIL], high-grade squamous intraepithelial lesions [HSIL], atypical glandular cells [AGC], and adenocarcinoma in situ [AIS]). Clinic providers collected a second sample of cervical ecto- and endocervical cells by using the Digene Cervical Sampler (Digene cervical brush and specimen transport medium; Digene, Gaithersburg, Maryland); this second sample was tested for high-risk HPV DNA by both Hybrid Capture 2 assay and L1 consensus polymerase chain reaction (PCR).

Thirteen human subjects committees (12 at local institutions and 1 at the Centers for Disease Control and Prevention [CDC]) reviewed and approved the study protocol. All women provided written informed consent before enrollment. All providers received the results of Hy-

brid Capture 2 testing and referred patients for further medical care on the basis of practices at the individual clinics. The HSS project investigators created counseling messages for use in reporting Hybrid Capture 2 and Pap test results to enrollees by consensus, on the basis of messages developed by the American Social Health Association and the most current guidelines available at the time (8).

Laboratory Testing

Investigators tested the samples for high-risk HPV DNA at 7 local laboratories in the 6 cities by using the Hybrid Capture 2 high-risk probe according to manufacturer instructions. The Hybrid Capture 2 high-risk probe gives a positive result in the presence of any 1 of 13 high-risk HPV types (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, or 68); however, individual HPV types are not identified.

Before Hybrid Capture 2 testing, we removed an aliquot from each cervical sample and sent it to CDC for HPV detection and typing based on L1 consensus PCR and the prototype Roche line blot assay (reagents provided by Roche Molecular Systems, Pleasanton, California). We provide only the results of Hybrid Capture 2 testing here; the results of PCR testing will be reported separately.

Statistical Analysis

We determined high-risk HPV prevalence by using Hybrid Capture 2 testing and calculated 95% CIs by using the binomial method. We calculated high-risk HPV prevalence by age, race, ethnicity, clinic type, city, and Pap test result, and age-adjusted prevalence by race, ethnicity, city, and clinic type. Prevalence data by Pap test result were stratified, not adjusted, for age (by groupings according to cervical screening recommendations) to report the observed prevalence in these categories.

We indirectly standardized our findings by using the total number of persons entered in the HSS project from all cities as the standard population. We calculated estimates of HPV prevalence per 100 persons by city (adjusting for age and clinic type), and by clinic type (adjusting for age and city). We assumed that the number of high-risk HPV cases followed a binomial distribution. We then calculated 95% CIs for these estimates (9). All analyses were performed in SAS, version 9.1 (SAS Institute, Cary, North Carolina).

Role of the Funding Source

All funding for this project was provided by CDC, Atlanta, Georgia. The funding source was involved in the design, conduct, and reporting of the study, as well as the decision to submit this manuscript for publication.

RESULTS

Study Population

Between 1 January 2003 and 31 December 2005, 10 427 women from all cities were eligible to enroll in the HSS project; only 219 (2%) declined. Of the 10 208 women who enrolled, we excluded 551 records from the analysis (5%) because of invalid HPV DNA test results (either Hybrid Capture 2 or PCR): 236 (2%) had invalid results on both Hybrid Capture 2 and PCR, 298 (3%) had invalid PCR results alone, and 17 (0.2%) had invalid Hybrid Capture 2 results alone. Among the 253 invalid Hybrid Capture 2 results, all were missing valid result data. The 9657 women with valid Hybrid Capture 2 and PCR

Table 1. **Prevalence of High-Risk Human Papillomavirus, by Demographic Characteristics and Cytology Results***

Characteristic	Enrollees, *n* (%)	High-Risk HPV Prevalence (95% CI), %†
Total	9657 (100)	23 (22–24)
Age group		
14–19 y	1240 (13)	35 (32–38)
20–29 y	4605 (48)	29 (28–30)
30–39 y	2016 (21)	13 (12–15)
40–49 y	1248 (13)	11 (9–13)
50–65 y	548 (6)	6 (4–8)
Race		
White	4642 (48)	23 (22–24)
African American	2438 (25)	25 (23–27)
Asian or Pacific Islander	957 (10)	17 (15–20)
American Indian or Alaskan Native	180 (2)	25 (19–32)
Multiracial	212 (2)	32 (25–38)
Unknown	1228 (13)	20 (17–22)
Ethnicity		
Hispanic	2290 (24)	20 (19–22)
Non-Hispanic	7259 (75)	24 (23–25)
Unknown	108 (1)	21 (14–30)
Clinic type		
Sexually transmitted disease	3009 (31)	27 (26–29)
Family planning	3493 (36)	26 (25–28)
Primary care	3155 (33)	15 (14–16)
City		
Boston, Massachusetts	2048 (21)	22 (20–24)
Baltimore, Maryland	1388 (14)	23 (21–25)
New Orleans, Louisiana‡	734 (8)	21 (18–24)
Seattle, Washington	1854 (19)	24 (22–26)
Denver, Colorado	1855 (19)	27 (25–29)
Los Angeles, California	1778 (18)	19 (17–21)
Cytology results		
Normal	8055 (86)	17 (16–17)
ASC-US	722 (8)	44 (40–47)
ASC-H	34 (0.4)	56 (38–73)
LSIL	446 (5)	88 (85–91)
HSIL	54 (0.6)	91 (80–97)
AGC	29 (0.3)	17 (6–36)
AIS	1 (<0.1)	100 (3–100)

*AGC = atypical glandular cells; AIS = adenocarcinoma in situ; ASC-H = atypical squamous cells—cannot exclude high-grade squamous intraepithelial lesion; ASC-US = atypical squamous cells of undetermined significance; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion.
† Prevalence based on Hybrid Capture 2 testing (Digene, Gaithersburg, Maryland).
‡ Enrollment was stopped in August 2005 because of Hurricane Katrina.

results for high-risk HPV comprised the sample for analysis.

Enrollment distribution across the 6 cities ranged from 734 to 2048 women (**Table 1**). About 61% of enrolled women were younger than 30 years of age, and 48% were white. Enrollment was equally distributed across STD and primary care clinics (31% and 33%, respectively) but was slightly higher in family planning clinics (36%). Only 26 (0.3%) enrollees were known to be HIV positive (either by self-report or documentation in medical record). We did not perform HIV testing on study participants as part of the HSS project.

High-Risk HPV Prevalence

Overall prevalence of high-risk HPV was 23% (2202 of 9657 women); all reported figures for high-risk HPV prevalence were obtained by Hybrid Capture 2 testing (**Table 1**). Prevalence was highest among women 14 to 19 years of age (35%) and declined with increasing age; the largest declines occurred between the 20- to 29-year and 30- to 39-year age groups and the 40- to 49-year and 50- to 65-year age groups. Unadjusted high-risk HPV prevalence across racial groups ranged from 17% to 32%. After age adjustment, we observed smaller differences in high-risk HPV prevalence between white persons (22% [CI, 21% to 24%]), African-American persons (24% [CI, 22% to 27%]), Asian persons and Pacific Islanders (23% [CI, 19% to 28%]), American Indians and Alaskan Natives (23% [CI, 16% to 33%]), multiracial persons (32% [CI, 24% to 44%]), and those of unknown race (20% [CI, 17% to 22%]). Unadjusted high-risk HPV prevalence was slightly higher among those of non-Hispanic ethnicity; this finding was also observed when age-adjusted prevalence in Hispanic persons (20% [CI, 18% to 23%]) was compared with that of non-Hispanic persons (24% [CI, 22% to 25%]). Of the 26 HIV-positive women enrolled, 12 (46%) were also positive for high-risk HPV. Prevalence across cities ranged from 19% to 27%. Age- and city-adjusted prevalence of high-risk HPV was highest in STD clinics (26% [CI, 24% to 29%]), followed by family planning clinics (24% [CI, 22% to 26%]), and was lowest in primary care clinics (17% [CI, 16% to 20%]) (**Table 2**).

Prevalence and Cervical Cytology

Approximately 14% of women had an abnormal Pap test result on the day of study enrollment (**Table 1**). High-risk HPV prevalence increased with increasing severity of Pap test abnormalities. Women with normal Pap tests had the lowest high-risk HPV prevalence (17%), but this subgroup included the largest number of women who tested positive for high-risk HPV by Hybrid Capture 2 (n = 1334). Women with LSIL had the second-largest number of positive results (n = 394), followed by women with ASC-US (n = 315). Women age 30 years or older had a prevalence of lower high-risk HPV than women younger than age 30 years for all Pap test result categories (**Tables 3** and 4); this observation was consistent across STD, family planning, and primary care clinics.

Prevalence in Selected Groups Recommended for Reflex or Co-Testing

Women with ASC-US

Women 21 to 65 years of age whose Pap tests showed ASC-US had a 38% prevalence of high-risk HPV by Hybrid Capture 2 testing. Among the 319 women age 21 to 29 years with ASC-US, 49% (155 of 319) tested positive for high-risk HPV infection by Hybrid Capture 2 and would be considered for colposcopy referral. Among women age 14 to 20, 21 to 24, and 25 to 29 years who had ASC-US, high-risk HPV prevalence by Hybrid Capture 2 testing was 62%, 50%, and 46%, respectively (**Table 3**).

Women Age 30 Years or Older with Normal Pap Test Results

Nine percent (304 of 3693) of women 30 years of age or older with normal Pap test results had high-risk HPV infection according to Hybrid Capture 2 testing (**Table 4**). The range in this observed value across the 3 clinic types was small (primary care, 8%; family planning, 9%; and

Table 2. **Adjusted High-Risk Human Papillomavirus Prevalence, by City and Clinic Type***

City	High-Risk HPV Prevalence (95% CI), %†			
	STD Clinics	Family Planning Clinics	Primary Care Clinics	Overall Age- and Clinic Type–Adjusted Prevalence
Boston, Massachusetts	20 (16–25)	24 (20–28)	8 (6–12)	19 (17–21)
Baltimore, Maryland	24 (19–30)	38 (30–49)	14 (11–18)	24 (21–28)
New Orleans, Louisiana	16 (6–37)	23 (17–30)	13 (10–17)	19 (15–22)
Seattle, Washington	30 (24–36)	28 (23–33)	14 (10–19)	24 (21–27)
Denver, Colorado	37 (31–44)	32 (25–40)	16 (13–21)	28 (25–32)
Los Angeles, California	25 (21–31)	20 (16–26)	22 (17–28)	23 (20–26)
Overall age- and city-adjusted prevalence	26 (24–29)	24 (22–26)	17 (16–20)	23 (22–24)†

*HPV = human papillomavirus; STD = sexually transmitted disease.
† Prevalence based on Hybrid Capture 2 testing (Digene, Gaithersburg, Maryland) in 9764 women.
‡ Unadjusted prevalence is presented.

Table 3. **High-Risk Human Papillomavirus Prevalence, by Cytology Result***

Age	Normal		ASC-US		ASC-H or AGC		LSIL, HSIL, or AIS	
	Enrollees, *n (%)*	High-Risk HPV Prevalence (95% CI), %†	Enrollees, *n (%)*	High-Risk HPV Prevalence (95% CI), %†	Enrollees, *n (%)*	High-Risk HPV Prevalence (95% CI), %†	Enrollees, *n (%)*	High-Risk HPV Prevalence (95% CI), %†
14–20 y	1418 (15)	24 (22–27)	161 (2)	62 (54–70)	8 (<1)	63 (24–91)	180 (2)	92 (87–95)
21–24 y	1820 (19)	24 (22–26)	177 (2)	50 (43–58)	12 (<1)	67 (35–90)	159 (2)	92 (86–96)
25–29 y	1463 (16)	17 (15–19)	142 (2)	46 (38–55)	10 (<1)	60 (26–88)	98 (1)	89 (81–94)
30–34 y	989 (11)	11 (9–13)	83 (1)	34 (24–45)	6 (<1)	17 (<1–64)	25 (<1)	80 (59–93)
35–39 y	767 (8)	9 (7–11)	56 (1)	23 (13–36)	4 (<1)	0 (0–60)	13 (<1)	62 (32–86)
40–44 y	611 (7)	9 (7–12)	45 (<1)	27 (15–42)	10 (<1)	20 (3–56)	13 (<1)	77 (46–95)
45–49 y	476 (5)	10 (7–13)	35 (<1)	11 (3–27)	8 (<1)	13 (<1–53)	9 (<1)	67 (30–93)
50–54 y	267 (3)	8 (5–12)	15 (<1)	7 (<1–32)	4 (<1)	25 (1–81)	3 (<1)	67 (9–99)
55–59 y	167 (2)	4 (1–8)	7 (<1)	29 (4–71)	1 (<1)	0 (0–98)	1 (<1)	0 (0–98)
60–65 y	77 (1)	0 (0–5)	1 (<1)	0 (0–98)	0 (0)	NA	0 (0)	NA
Total	8055 (86)	–	722 (8)	–	63 (1)	–	501 (5)	–

* Based on data from 9341 women. AGC = atypical glandular cells; AIS = adenocarcinoma in situ; ASC-H = atypical squamous cells—cannot exclude high-grade squamous intraepithelial lesion; ASC-US = atypical squamous cells of undetermined significance; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion; NA = not applicable.
† Percentage of total HPV Sentinel Surveillance project sample with Papanicolaou tests (9341 of 9657 women).

STD, 11%). The youngest women in this category, those 30 to 34 years of age, had the highest prevalence of high-risk HPV (11%) of any age group (**Table 3**). Prevalence remained 8% to 10% among women with normal Pap tests through 54 years of age. High-risk HPV prevalence was 4% among women 55 to 59 years of age, and no high-risk HPV was detected among women 60 to 65 years of age.

Discussion

Our findings document the substantial number of high-risk HPV infections that Hybrid Capture 2 testing would detect among women presenting for cervical screening at STD, family planning, and primary care clinics in the United States. The overall prevalence of 23% shown by Hybrid Capture 2 testing and the large number of infections across demographic groups, clinic types, and cities is indicative of the high prevalence of high-risk HPV (although most infections will not result in cervical disease, particularly among adolescents [10, 11]). Of age, race, ethnicity, clinic type, and city categories, high-risk HPV prevalence differed most by age (range, 6% to 35%). The observed distribution of steadily decreasing high-risk HPV prevalence across increasing age groups is consistent with that observed in other studies in the United States and other developed countries with cervical screening programs (12). In contrast, other countries exhibited U-shaped prevalence curves or flat curves (that is, high HPV prevalence with no decrease in older groups). Observed variations are most likely due to differences in the availability of cervical screening programs, in incidence of HPV infections, and in sexual behaviors. In contrast to known epidemiologic associations between race and other sexually transmitted infections (13–15), the age-adjusted prevalence of high-risk HPV infection did not vary substantially by race (range, 20% to 24%, excluding the prevalence of 32% observed among multiracial women) or ethnicity (range, 20% to 24%) but did vary more by clinic type (range, 17% to 26%, adjusted for age and city). The range in prevalence across cities was 19% to 28% (adjusted for age and clinic type). Analyses are planned to further evaluate these observed differences.

Our high-risk HPV prevalence estimates for women age 20 to 29 years are higher than those reported from ADHEALTH (National Longitudinal Study of Adolescent Health) (20% vs. 29% in the HSS project) (16), and we observed a higher overall prevalence of high-risk HPV than that in NHANES (National Health and Nutrition Examination Survey) (15% among women age 14 to 59 years vs. 23% in the HSS project) (17). The highest prevalence reported in NHANES was approximately 30% for women 20 to 24 years of age, whereas we observed the highest prevalence (35%) in women 14 to 19 years of age. Differences in the age-specific prevalence of high-risk HPV among the HSS project, ADHEALTH, and NHANES samples are likely due to the different populations sampled (the HSS project enrolled a higher proportion of sexually experienced adolescent females and more sexually active women in all age groups) and differing specimen types and methods for specimen collection and HPV testing (Hybrid Capture 2 testing of provider-collected cervical samples in the HSS project, PCR testing of self-collected vaginal swabs in NHANES, and urine-based PCR testing in ADHEALTH).

Although African-American women and Hispanic women account for a disproportionate burden of cervical cancer cases and deaths in the United States compared with white women and non-Hispanic women, respectively

Table 4. **High-Risk Human Papillomavirus Prevalence, by Age, Clinic Type, and Cytology Result***

Clinic Type and Cytology Result	Age <30 y		Age ≥30 y	
	Women Tested, *n*	High-Risk HPV Prevalence (95% CI), %†	Women Tested, *n*	High-Risk HPV Prevalence (95% CI), %†
STD				
Normal	1551	26 (24–28)	844	11 (9–13)
ASC-US	165	55 (47–62)	71	23 (13–34)
ASC-H or AGC	13	69 (39–91)	12	17 (2–48)
LSIL, HSIL, or AIS	150	92 (86–96)	25	76 (55–91)
Family planning				
Normal	2091	23 (21–25)	783	9 (7–11)
ASC-US	234	52 (46–59)	56	30 (19–44)
ASC-H or AGC	9	78 (40–97)	4	25 (1–81)
LSIL, HSIL, or AIS	207	93 (89–96)	13	77 (46–95)
Primary care				
Normal	1059	15 (13–17)	1727	8 (7–10)
ASC-US	81	53 (42–64)	115	23 (16–32)
ASC-H or AGC	8	38 (9–76)	17	12 (1–36)
LSIL, HSIL, or AIS	80	84 (74–91)	26	65 (44–83)
All types				
Normal	4701	22 (21–23)	3354	9 (8–10)
ASC-US	480	53 (49–58)	242	25 (19–31)
ASC-H or AGC	30	63 (44–80)	33	15 (5–32)
LSIL, HSIL, or AIS	437	91 (88–94)	64	72 (59–82)

* AGC = atypical glandular cells; AIS = adenocarcinoma in situ; ASC-H = atypical squamous cells—cannot exclude high-grade squamous intraepithelial lesion; ASC-US = atypical squamous cells of undetermined significance; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion; STD = sexually transmitted disease.
† Prevalence based on Hybrid Capture 2 testing (Digene, Gaithersburg, Maryland).

(18), HSS project data do not demonstrate large differences in high-risk HPV prevalence across these racial or ethnic groups after age adjustment. This suggests that differential rates of cervical cancer may be due to differences in the natural history of the infections across racial and ethnic groups (19) or to differences in the diagnosis and care of African-American and Hispanic women (20).

The distribution of Pap test results in the HSS project and the prevalence of high-risk HPV shown by Hybrid Capture 2 testing in each cytology category are consistent with data presented in other published reports (21) and higher than estimates from an unpublished report (high-risk HPV prevalence of 3.8% in women age ≥30 years in a managed care population) (Kinney W. Personal communication, 24 September 2007). Among women whose Pap tests showed ASC-US, Hybrid Capture 2 testing showed high-risk HPV infection in more than 50% of those younger than 30 years and 25% of those age 30 years or older. Previous cost analyses (based on prevalence estimates similar to those in the HSS project) have demonstrated the cost-effectiveness of reflex testing for high-risk HPV in women with ASC-US (22). The HSS data indicate that these observations can be extended to geographically and racially and ethnically diverse clinic populations in the United States.

We observed substantial high-risk HPV prevalence (17%) among women with normal Pap test results. Among those age 30 years or older who had normal Pap test results, high-risk HPV prevalence on Hybrid Capture 2 testing was 9% (304 of 3354). Because this age group is targeted for co-testing with Pap and Hybrid Capture 2 testing, our findings suggest that 8% (304 of 3693) of all women age 30 years or older in the U.S. cervical screening population would fall into this category (normal Pap test, high-risk HPV–positive) and would be recommended for repeated Pap and Hybrid Capture 2 testing in 12 months. A recent study demonstrated the usefulness of HPV DNA co-testing (with PCR) for Swedish women in their mid-30s (23). Cost-effective analyses of HSS project data may be used to inform the appropriateness of U.S. screening guidelines regarding co-testing with Hybrid Capture 2 for women at least 30 years of age with normal Pap test results.

The HSS project data may also be used to inform decisions regarding appropriate age groups for reflex testing with Hybrid Capture 2 among women with ASC-US. In the HSS project, Hybrid Capture 2 testing demonstrated high-risk HPV infection in half of women age 21 to 24 years (a group recommended for reflex testing), similar to the prevalence observed among those age 14 to 20 years (a group not recommended for reflex testing).

Hybrid Capture 2 testing demonstrates very low prevalence of high-risk HPV among women age 50 years or older. Our data inform the appropriateness of cervical screening and Hybrid Capture 2 testing of these women, in

whom colposcopy is difficult and the rate of cervical cancer precursor lesions is low in countries with well-screened populations (such as the United States). Of note, however, only 6% of women (548 women) in the HSS project sample were 50 years of age or older.

An important finding was the similarity in high-risk HPV prevalence on Hybrid Capture 2 testing in groups recommended for reflex testing or co-testing across STD, family planning, and primary care clinics. Despite presumptive differences in sexual risk among women attending these 3 clinic types and the observed 12–percentage point difference in overall high-risk HPV prevalence between the clinic type with the lowest prevalence (15%) and that with the highest prevalence (27%), the observed ranges in prevalence of high-risk HPV among women recommended for co-testing (52% to 55%) and among women recommended for reflex testing (8% to 11%) were unexpectedly small across clinic types. These small differences suggest that prevalence in these specific groups may not vary according to a woman's sexual risk.

Enrollment in the HSS project required informed consent. This did not seem to negatively affect enrollment, because the overall refusal rate was low (2%). Laboratory evaluations of Pap tests and Hybrid Capture 2 were not centralized (7 different laboratories). However, all protocols for specimen handling and data interpretation were standardized across participating laboratories. Furthermore, Pap and Hybrid Capture 2 results in the HSS project reflect real-world conditions of test performance and interpretation. The HSS project was not population-based, and our results cannot be generalized to the general population of women in the United States; however, our findings can be generalized to the millions of women receiving care in similar clinics throughout the country (the cervical screening population).

Our findings demonstrate the widespread prevalence of high-risk HPV among a group of women with a diverse demographic composition. These data are important for examining the strengths and weaknesses of various cervical screening strategies and may have implications for the future direction of cervical screening recommendations.

From the Centers for Disease Control and Prevention, Atlanta, Georgia; University of Washington, Seattle, Washington; Massachusetts Department of Public Health, Boston, Massachusetts; Denver Public Health, Denver, Colorado; County of Los Angeles Department of Health Services, Los Angeles, California; Johns Hopkins University School of Medicine, Baltimore, Maryland; and Louisiana State University Health Sciences Center, New Orleans, Louisiana.

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Requests for Single Reprints: S. Deblina Datta, MD, Centers for Disease Control and Prevention, 1600 Clifton Road, MS E-02, Atlanta, GA 30333; e-mail, ddatta@cdc.gov.

Current author addresses and author contributions are available at www.annals.org.

References

1. **U.S. Cancer Statistics Working Group.** United States Cancer Statistics: 2004 Incidence and Mortality. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; 2007. Accessed at www.cdc.gov/cancer/npcr/npcrpdfs/US_Cancer_Statistics_2004_Incidence_and_Mortality.pdf on 8 February 2008.

2. Screening for Cervical Cancer. Rockville, Maryland: U.S. Preventive Services Task Force; 2003. Accessed at www.ahrq.gov/clinic/uspstf/uspscerv.htm on 8 February 2008.

3. **Saslow D, Runowicz CD, Solomon D, Moscicki AB, Smith RA, Eyre HJ, et al.** American Cancer Society. American Cancer Society guideline for the early detection of cervical neoplasia and cancer. CA Cancer J Clin. 2002;52:342-62. [PMID: 12469763]

4. **ACOG Committee on Practice Bulletins.** ACOG Practice Bulletin: clinical management guidelines for obstetrician-gynecologists. Number 45, August 2003. Cervical cytology screening (replaces committee opinion 152, March 1995). Obstet Gynecol. 2003;102:417-27. [PMID: 12907124]

5. **Bosch FX, Muñoz N.** The viral etiology of cervical cancer. Virus Res. 2002; 89:183-90. [PMID: 12445658]

6. **Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al.** Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999;189:12-9. [PMID: 10451482]

7. **Wright TC, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D.** 2006 American Society for Colposcopy and Cervical Pathology-sponsored Consensus Conference. 2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests. Am J Obstet Gynecol. 2007;197: 346-55. [PMID: 17904957]

8. Frequently Asked Questions About Cervical Cancer/HPV Vaccine Access in the U.S. Research Triangle Park, NC: American Social Health Organization; 2007. Accessed at www.ashastd.org/pdfs/HPV_FAQ_032007.pdf on 8 February 2008.

9. **Armitage P, Berry G, Matthews JN.** Statistical Methods in Medical Research, 4th ed. Oxford: Blackwell Publishing; 2002.

10. **Moscicki AB, Ellenberg JH, Farhat S, Xu J.** Persistence of human papillomavirus infection in HIV-infected and -uninfected adolescent girls: risk factors and differences, by phylogenetic type. J Infect Dis. 2004;190:37-45. [PMID: 15195241]

11. **Castle PE, Schiffman M, Herrero R, Hildesheim A, Rodriguez AC, Bratti MC, et al.** A prospective study of age trends in cervical human papillomavirus acquisition and persistence in Guanacaste, Costa Rica. J Infect Dis. 2005;191: 1808-16. [PMID: 15871112]

12. **Franceschi S, Herrero R, Clifford GM, Snijders PJ, Arslan A, Anh PT, et al.** Variations in the age-specific curves of human papillomavirus prevalence in women worldwide. Int J Cancer. 2006;119:2677-84. [PMID: 16991121]

13. **Fleming DT, McQuillan GM, Johnson RE, Nahmias AJ, Aral SO, Lee FK, et al.** Herpes simplex virus type 2 in the United States, 1976 to 1994. N Engl J Med. 1997;337:1105-11. [PMID: 9329932]
14. **Datta SD, Sternberg M, Johnson RE, Berman S, Papp JR, McQuillan G, et al.** Gonorrhea and chlamydia in the United States among persons 14 to 39 years of age, 1999 to 2002. Ann Intern Med. 2007;147:89-96. [PMID: 17638719]
15. **Gottlieb SL, Pope V, Sternberg MR, McQuillan GM, Beltrami JF, Berman SM, et al.** Prevalence of syphilis seroreactivity in the United States: data from the National Health and Nutrition Examination Surveys (NHANES) 2001-2004. Sex Transm Dis. 2008. [Forthcoming]
16. **Manhart LE, Holmes KK, Koutsky LA, Wood TR, Kenney DL, Feng Q, et al.** Human papillomavirus infection among sexually active young women in the United States: Implications for developing a vaccination strategy. Sex Transm Dis. 2006;33:502-8. [PMID: 16572039]
17. **Dunne EF, Unger ER, Sternberg M, McQuillan G, Swan DC, Patel SS, et al.** Prevalence of HPV infection among females in the United States. JAMA. 2007;297:813-9. [PMID: 17327523]
18. **Saraiya M, Ahmed F, Krishnan S, Richards TB, Unger ER, Lawson HW.** Cervical cancer incidence in a prevaccine era in the United States, 1998-2002. Obstet Gynecol. 2007;109:360-70. [PMID: 17267837]
19. **Xi LF, Kiviat NB, Hildesheim A, Galloway DA, Wheeler CM, Ho J, et al.** Human papillomavirus type 16 and 18 variants: race-related distribution and persistence. J Natl Cancer Inst. 2006;98:1045-52. [PMID: 16882941]
20. **Yabroff KR, Lawrence WF, King JC, Mangan P, Washington KS, Yi B, et al.** Geographic disparities in cervical cancer mortality: what are the roles of risk factor prevalence, screening, and use of recommended treatment? J Rural Health. 2005;21:149-57. [PMID: 15859052]
21. **Kulasingam SL, Hughes JP, Kiviat NB, Mao C, Weiss NS, Kuypers JM, et al.** Evaluation of human papillomavirus testing in primary screening for cervical abnormalities: comparison of sensitivity, specificity, and frequency of referral. JAMA. 2002;288:1749-57. [PMID: 12365959]
22. **Kulasingam SL, Kim JJ, Lawrence WF, Mandelblatt JS, Myers ER, Schiffman M, et al. ALTS Group.** Cost-effectiveness analysis based on the Atypical squamous cells of undetermined significance/Low-grade squamous intraepithelial lesion Triage Study (ALTS). J Natl Cancer Inst. 2006;98:92-100. [PMID: 16418511]
23. **Naucler P, Ryd W, Törnberg S, Strand A, Wadell G, Elfgren K, et al.** Human papillomavirus and Papanicolaou tests to screen for cervical cancer. N Engl J Med. 2007;357:1589-97. [PMID: 17942872]

Current Author Addresses: Drs. Datta, Unger, and Weinstock and Ms. Suhr: Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30333.
Drs. Koutsky and Weaver: University of Washington, 1914 North 34th Street, Suite 300, Seattle, WA 98103.
Dr. Shlay: Denver Public Health, 605 Bannock Street, Denver, CO 80204.
Drs. McClain, Kerndt, and Zenilman: County of Los Angeles Department of Health Services, STD Program, 2615 South Grand Avenue, Room 500, Los Angeles, CA 90007.
Dr. Hagensee: Louisiana State University Health Sciences Center, 190 Perdido Street, New Orleans, LA 70112.

Author Contributions: Conception and design: S.D. Datta, L.A. Koutsky, E.R. Unger, J. Shlay, T. McClain, B. Weaver, P. Kerndt, J. Zenilman, M. Hagensee, H. Weinstock.
Analysis and interpretation of the data: S.D. Datta, L.A. Koutsky, E.R. Unger, J. Shlay, T. McClain, P. Kerndt, J. Zenilman, C.J. Suhr.
Drafting of the article: S.D. Datta, L.A. Koutsky, E.R. Unger.
Critical revision of the article for important intellectual content: S.D. Datta, L.A. Koutsky, E.R. Unger, J. Shlay, T. McClain, B. Weaver, P. Kerndt, J. Zenilman, M. Hagensee, H. Weinstock.
Final approval of the article: S.D. Datta, L.A. Koutsky, E.R. Unger, J. Shlay, T. McClain, B. Weaver, P. Kerndt, J. Zenilman, H. Weinstock.
Provision of study materials or patients: S.D. Datta, L.A. Koutsky, J. Shlay, T. McClain, B. Weaver, J. Zanilman, M. Hagensee.
Statistical expertise: S.D. Datta, L.A. Koutsky.
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Collection and assembly of data: J. Zenilman.