Seroprevalence of Human Papillomavirus Type 16 Infection in the United States

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Infection with human papillomavirus (HPV) type 16 accounts for about half of cervical cancers worldwide. This study investigated the seroepidemiology of HPV-16 infection in the United States by using a population-based survey. Serum samples and questionnaire data were collected from 1991 to 1994 for the National Health and Nutrition Examination Surveys. HPV-16–specific IgG antibody was detected by use of an HPV-16 virus-like particle ELISA. HPV-16 seropositivity in the US population aged 12–59 years was 13.0% (95% confidence interval, 11.5%–14.7%). Seroprevalence was higher in women (17.9%) than in men (7.9%). Age, race/ethnicity, and number of lifetime sex partners were associated with HPV seropositivity in women. Race/ethnicity, age at first intercourse, urban/nonurban residence, years of sexual activity, and having had sex with a man were associated with HPV seropositivity in men. Information on HPV-16 seroepidemiology will be important for designing prevention efforts including vaccine programs.

Genital human papillomavirus (HPV) infection is the most common sexually transmitted infection in the United States [1, 2]. At least 30 HPV types infect the genital area, and persistent infection with high-risk HPV types is the strongest risk factor for cervical cancer. High-risk HPV types, including 16, 18, 31, 33, and 35, are found in up to 93% of cervical cancers worldwide, and HPV-16 accounts for 50% [3–6].

Assessing the extent of genital HPV infection in the US population has been difficult for many reasons. HPV does not grow in tissue culture, closely related types cause different diseases (e.g., cervical cancer and genital warts), and most infections are asymptomatic. No surveillance systems exist, and no large population-based prevalence surveys have been feasible. Current knowledge of HPV prevalence and risk factors is based largely on measuring viral DNA in genital epithelial cells. However, HPV DNA detection is limited by sampling methodology and reflects only current status; HPV DNA becomes undetectable within 2 years in most women [7]. Serologic testing is a better measure of cumulative exposure, and type-specific serologic assays have become available in recent years. Correlations between assays for IgG antibodies to HPV-16 capsids and detection of HPV DNA, high-grade cervical neoplasia, and number of lifetime sex partners indicate that seroassays are useful epidemiologic research tools [8–10].

Seroepidemiologic data also are useful for establishing prevalence of infection in the general population and for identifying groups at highest risk for targeting prevention and clinical services. We report here the results of a national seroepidemiologic survey of HPV-16 infection performed on surplus serum samples from the second phase of the third National Health and Nutrition Examination Survey (NHANES III), conducted from 1991 to 1994.

Methods

Study populations and study design. The NHANES is a series of cross-sectional national surveys conducted by the National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC). These surveys use a complex, stratified, multistage, probability cluster design to select a representative sample of the US civilian noninstitutionalized population [11].

NHANES III was conducted in 1988–1994 in 2 3-year phases. NHANES III oversampled children aged <5 years, persons aged ≥60 years, Mexican Americans, and blacks. For this analysis, race/ethnicity was defined by self-report as non-Hispanic white and non-Hispanic black (referred to as “white” and “black” in the text), and...
Mexican American. Persons who did not identify themselves in these categories were classified as “other.” The poverty index was calculated by dividing the total family income by the poverty threshold, as defined by the US Census [12], with adjustment for family size at the time of the interview. Urban residence was defined as residing in a county in a metropolitan area; all other counties were defined as “nonurban.” Limited sexual history questions were asked of adolescents aged 15–16 years. A more extensive sexual behavior questionnaire was administered to participants aged 17–59 years. Alcohol, cocaine, and marijuana use questions were asked of study subjects aged ≥12 years.

Response rates in the NHANES III have been described elsewhere [13]. We tested serum samples available from the second phase of the NHANES III conducted during 1991–1994. Of the 9629 subjects selected to participate in the survey in the 12- to 59-year age group, 7476 (77.6%) agreed to the examination; from these participants, 7218 serum samples were available for HPV testing (96.5% of examined persons).

Serologic testing. Serologic testing for HPV-16 was performed at the CDC. Virus-like particles (VLPs) were produced by expression of an HPV-16 L1 recombinant baculovirus in insect cells, as described elsewhere [14, 15]. ELISAs were standardized and performed as described elsewhere [14]. In brief, purified VLPs were pooled as a single lot sufficient to complete the entire study and were aliquoted and frozen at −70°C until use. Microwell plates (Immulon II; Dynatech Laboratories) were coated overnight with 0.1 μg/well VLPs. Plates were washed with PBS + 0.1% Tween 20 (PBST) and were blocked for 1 h with diluent (10 mM Tris plus 0.15 M NaCl [pH 8.0], 10% goat serum [Life Technologies], 50% SuperBlock [Pierce]) containing 0.5% Tween 20. Plates were washed with PBST and were incubated with 50 μL of serum (1:20 in diluent plus 10% insect cell lysate) per well at 37°C for 1 h. Plates were again washed with PBST and were detected by use of alkaline phosphatase-conjugated goat anti-human IgG antibody (Roche Molecular Biochemicals) and alkaline phosphatase substrate (Phosphatase; Sigma). Raw absorbance values were detected at 405 nm in an automated plate reader (Dynex MRX II Revelation). Each serum sample was tested in duplicate wells. For a given sample, if the SD of the absorbance value of either well was ≥25% of the mean absorbance value of the duplicate wells, testing was repeated.

For quality control and evaluation, we used known positive and negative human serum samples (gifts of M. Hagensee, Louisiana State University, and H. Strickler, National Cancer Institute [now at Albert Einstein School of Medicine]). Additional negative serum samples were obtained from Egleston Children’s Hospital (Atlanta). Control serum samples also were used to prepare pools of high-positive, low-positive, and negative serum controls. The pooled controls were used to monitor day-to-day and plate-to-plate variation.

Results for individual control serum samples that were run throughout the course of the NHANES III analysis were used in receiver operating characteristic (ROC) analysis to determine the ELISA cutoff value for discrimination between positive and negative samples [14, 16]. Evaluation of ROC plots indicated that a cutoff value of 0.64 absorbance resulted in 93% sensitivity and 98.5% specificity. Type-specific serologic testing for herpes simplex virus (HSV) types 1 and 2 was performed at Emory University by immunodot assays based on purified glycoproteins gG1 and gG2 by methods described elsewhere [17, 18].

Statistical analysis. We explored bivariate associations with HPV seropositivity and the following demographic, social, sexual, and reproductive variables for women and men separately: age, marital status, race/ethnicity, residence, region (Northeast, Midwest, South, West), education level, poverty index, use of tobacco, alcohol, marijuana, or cocaine, early age at first intercourse (defined as <18 years), number of sex partners (lifetime and past year), years of sexual activity (calculated by subtracting age at first intercourse from age at study enrollment), and HSV-1 and HSV-2 seropositivity. In addition, for women we considered the number of live births, oral contraceptive use, and cervical cancer; for men, we considered whether the man reported ever having sex with other men.

Prevalence estimates were weighted to represent the total US population and to account for oversampling and nonresponse to the household interview and physical examination [19, 20]. Persons missing HPV test results were significantly younger than those with HPV results; therefore, the weights provided by NCHS were further adjusted by using the weighted proportion of response in each age group and then were poststratified by age, race/ethnicity, and sex. These adjusted weights were used for the prevalence estimates and for the logistic regression model to identify variables associated with HPV seropositivity. The confidence intervals (CIs) for the prevalence estimates were calculated on the basis of log transformation with the SE of the log prevalence calculated by use of the delta method [21]. The SEs for the prevalence estimates were obtained by using SUDAAN software [22]. Similarly, approximate SEs of prevalence ratios were calculated by use of the delta method based on the log of the prevalence ratio by use of SEs from SUDAAN.

We used logistic regression to determine variables that were independently associated with HPV-16 antibodies in sexually active men and women separately. Participants whose race/ethnicity category was “other” were excluded from these analyses because of small sample sizes. The initial logistic model included all demographic variables with a bivariate Wald χ² statistic P value ≤.05. After these variables were entered into the model, we used the Satterthwaite-adjusted χ² to determine statistical significance at the P = .05 level. Variables in the model that were statistically significant remained in the model; other variables were omitted if there was no evidence of data-based confounding (>30% change in the parameter estimate). A step-up logistic regression model was fitted where pairwise interactions were added to the remaining main effects in the logistic model and were considered to be statistically significant if the Satterthwaite-adjusted χ² P ≤ .05.

Results

Overall, 13.0% (95% CI, 11.5–14.7; table 1) of study participants aged 12–59 years had antibodies to HPV-16. Seroprevalence was significantly higher in women (17.9%) than in men (7.9%), yielding a female:male prevalence ratio of 2.3 (95% CI, 1.8–2.9). Seroprevalence was 12.5% among whites, 19.1% among blacks, and 8.9% among Mexican Americans. With increasing age, HPV-16 seroprevalence increased in women to 24.7% at ages 20–29 years and then declined to 11.0% after age 49 years. In
men, seroprevalence peaked later, at ages 30–39 years (11.5%) and was sustained throughout the older age groups.

In women, HPV-16 seropositivity was significantly associated with several variables (tables 1 and 2), including age, race/ethnicity, education, alcohol use, marijuana use (ever), cocaine use (ever), ever having sexual intercourse, early age at first intercourse, number of lifetime sex partners, number of sex partners during the past year, HSV-2 seropositivity, and oral contraceptive use (ever). These variables were further explored by logistic regression. No statistically significant differences in HPV-16 seropositivity were found for marital status, residence, poverty index, tobacco use, number of live births, years of sexual activity, and having sex with men remained statistically significant and were dropped from the model. No other variables were statistically significant or important confounding variables when added to this model.

In the logistic model, age, race/ethnicity, marijuana smoking (ever), and age at first sexual intercourse were significantly associated with HPV-16 seropositivity before adding number of lifetime sex partners into the model. However, after including number of lifetime partners in the model, marijuana smoking (ever) and age at first sexual intercourse were no longer statistically significant and were dropped from the model. No other variables were statistically significant or important confounding variables when added to this model.

Next, we fitted a step-up logistic regression model and added pairwise interactions to the main effects model. No pairwise interactions were statistically significant. Because of the limited degrees of freedom in this complex survey setting, age and number of lifetime partners were treated as continuous variables to assess any interactions. The final model appears in table 3.

In men, HPV-16 seropositivity was significantly associated with several variables (tables 1 and 2), including age, race/ethnicity, marital status, poverty index, residence, age at first intercourse, years of sexual activity, number of lifetime sex partners, number of sex partners during the past year, and having sex with a man. These variables were subsequently explored by logistic regression.

No statistically significant differences in HPV-16 seropositivity were found for region, education, tobacco use, cocaine use, alcohol use, ever having sex, or HSV-1 or -2 seropositivity. In the logistic model, we recoded age as a dichotomous variable (<30 years vs. ≥30 years), since the log odds estimates were similar for men aged 12–29 years, and for those aged ≥30 years. Demographic variables that remained statistically significant in the logistic model were age, residence, and race/ethnicity. The other demographic variables did not appear to be important confounding variables and hence were omitted from the model. Next, sexual variables with statistically significant bivariate associations were added. Only age at first sexual intercourse, years of sexual activity, and having sex with men remained statistically significant. No other variables appeared to be confounders. Although age was no longer statistically significant, it was retained in the final model since it appeared to be confounded with years of sexual activity. Next, a step-up logistic regression model was fitted where pairwise interactions were added to the main effects model. One interaction, race/ethnicity and residence, was statistically significant. The final logistic model appears in table 4.

### Discussion

These findings document the high levels of HPV-16 infection in the United States, especially in women. In each racial/ethnic group, seropositivity was at least 2 times higher in women than in men, and seropositivity was high even in women who reported only 1 sex partner over their lifetime. Differences in seropositivity between men and women were not unexpected, since anatomic and other biologic differences usually portend greater susceptibility to most sexually transmitted diseases for women than for men. For example, higher transmission risk from men to women for gonorrhea and HSV-2 [23–27] and higher population-based prevalence of gonorrhea, chlamydia, and HSV-2 seropositivity in women are well documented [17, 28]. However, the most likely explanation for higher HPV-16 seropositivity in women is that women and men have fundamental differences in immune response after exposure [29–33].

Previous studies [32–35] found higher HPV-16 seroprevalence and higher mean ELISA values for women than for men. In
Table 2. Human papillomavirus (HPV) type 16 seroprevalence, by demographic, behavioral, and sexual/reproductive factors.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Sample size, no.</th>
<th>Men (95% CI)</th>
<th>Prevalence ratio (95% CI)</th>
<th>Women (95% CI)</th>
<th>Prevalence ratio (95% CI)</th>
</tr>
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<td><strong>Demographic</strong></td>
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<td>Marital status</td>
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<td>1101</td>
<td>5.0 (3.6–6.9)</td>
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<td>Married</td>
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<td>1.9 (1.3–2.8)</td>
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<td>Divorced</td>
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<td>2.4 (1.1–5.2)</td>
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<td>Widowed</td>
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<td>1.1 (0.8–1.4)</td>
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<td><strong>Region</strong></td>
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<td>Midwest</td>
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<tr>
<td>South</td>
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<td>1.4 (0.8–2.5)</td>
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<tr>
<td>West</td>
<td>605</td>
<td>5.5 (3.0–9.8)</td>
<td>0.8 (0.4–1.7)</td>
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<tr>
<td>Residence</td>
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<td>10.3 (8.3–12.7)</td>
<td>1.9 (1.2–2.9)</td>
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<td>18.2 (15.0–21.9)</td>
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<td><strong>Behavioral</strong></td>
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<td>Ever used cocaine</td>
<td></td>
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<td>1.7 (1.0–2.9)</td>
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<td>Ever used marijuana</td>
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<td>1.6 (1.0–2.6)</td>
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<td>&lt;12 drinks in lifetime</td>
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<td>6.8 (4.0–11.5)</td>
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<td>&gt;12 drinks in lifetime</td>
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<td>Ever had sex</td>
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<td>177</td>
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<td>Age at first intercourse, years</td>
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<td>10–49</td>
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<td>≥50</td>
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<td>2.8 (1.2–6.5)</td>
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<td>10–16</td>
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<td>17–24</td>
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<td>6.8 (3.8–12.2)</td>
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<td><strong>HSV-2 serostatus</strong></td>
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<td>Seropositive</td>
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<td>11.4 (7.0–18.6)</td>
<td>1.5 (0.9–2.6)</td>
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<td>Seronegative</td>
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<td>Seropositive</td>
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<td>1.3 (0.8–2.2)</td>
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<tr>
<td>Seronegative</td>
<td>636</td>
<td>6.9 (4.6–10.3)</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral contraceptive use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Never</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td><strong>History of cervical cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>No</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
<td>—</td>
</tr>
<tr>
<td><strong>MSM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>42</td>
<td>37.7 (24.5–57.9)</td>
<td>4.6 (2.7–7.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>2366</td>
<td>8.1 (6.3–10.4)</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE. CI, confidence interval; HSV, herpes simplex virus; MSM, men who had sex with men; —, data not applicable.

* P < .05.

Coefficient of variation >30% (i.e., unreliable estimate).
men, HPV infections may be more transient, and infection in men often involves keratinized epithelium that may be less likely than mucosal epithelium to induce a humoral immune response [32, 34]. Anorectal mucosal exposure may be more likely to produce a detectable immune response and could contribute to the high seropositivity in men who had sex with men.

We found associations between HPV-16 seropositivity and sexual behavior in women and men, and age in women. Although HPV DNA detection is strongly age-dependent in women [2, 36, 37], seroprevalence studies in men and women have not shown consistent associations with age [8, 32–34, 38–41] and, in general, have not shown the expected linear associations that are consistently seen for HSV-2 infection [42]. The strong association between HPV-16 seropositivity and number of lifetime sex partners and no association with number of recent partners observed in our study have been reported elsewhere [8, 10, 32–34, 38, 39] and suggest seropositivity is a measure of lifetime rather than of recent exposure.

Seropositivity in persons who reported no sex partners may be explained by underreporting of sexual behavior [43, 44], vertical or other nonsexual transmission, including oral and nongenital infection [45–48], or false-positive serologic tests. Underreporting of sexual activity is likely, especially since the questionnaire did not define sexual intercourse. Oral-genital and manual-genital contact could transmit HPV infection yet might not be reported as sexual intercourse [43, 44, 49]. Low levels of HPV-16 seropositivity have been observed in those who have not had intercourse and children in previous studies that used similar serologic assays [50, 51].

The HPV-16 seroprevalence observed in our study probably underestimates the cumulative prevalence of HPV-16 infection in the United States for several reasons. First, not all persons who become infected with HPV-16 develop a serologic response. Previous studies in women showed that <60% of those with newly detectable HPV-16 DNA develop HPV-16 antibodies [52], with a median lag time to seroconversion of 11.8 months.

Second, duration of seropositivity is not well defined. A study of 11 women showed that levels of antibodies to HPV-16 persisted for the 7–13-year follow-up period [53]. Another study of 1656 pregnant women showed that antibody levels were stable during a 4-year follow-up period [54]. Whether persistence of antibodies differs across demographic groups has not been studied. We are not aware of any published data on persistence of antibodies in men.

Our findings have important public health implications for the development of cervical cancer prevention and control strategies. National HPV seroprevalence data will be valuable for HPV vaccine research and for development of HPV vaccine programs. Prophylactic vaccines for HPV-16 based on L1 virus-like particles show great promise, and vaccine development is well underway. Topics under debate include whether to vaccinate women only or perhaps men only, the ideal age at vaccination, and which types of HPV to include in a vaccine [55, 56]. Our national data on seroepidemiology of naturally occurring HPV-16 infection is useful to establish baseline HPV-16 seroprevalence in demographic groups, to highlight differences in humoral immune responses between men and women, and to document a high burden of infection with this single HPV type. Moreover, a system for monitoring seroprevalence over time will be valuable to assess effectiveness of vaccine programs.

Acknowledgments

We thank Cynthia Bierl for technical assistance, Joseph Icenogle for contributions to protocol development, and Rosane Nisenbaum for statistical analysis of receiver operating characteristic data.

### Table 3. Multivariate analyses of human papillomavirus (HPV) type 16 seropositivity in women.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>40–49</td>
<td>2.1 (1.4–3.2)</td>
</tr>
<tr>
<td>30–39</td>
<td>1.3 (0.9–1.8)</td>
</tr>
<tr>
<td>20–29</td>
<td>2.2 (1.3–3.6)</td>
</tr>
<tr>
<td>12–19</td>
<td>0.9 (0.6–1.5)</td>
</tr>
</tbody>
</table>

**NOTE.** CI, confidence interval.

<table>
<thead>
<tr>
<th>Race/ethnicity</th>
<th>Adjusted odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hispanic white</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>1.7 (1.3–2.3)</td>
</tr>
<tr>
<td>Mexican American</td>
<td>0.9 (0.7–1.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lifetime sex partners, no.</th>
<th>Adjusted odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>2–4</td>
<td>3.0 (1.7–5.2)</td>
</tr>
<tr>
<td>5–10</td>
<td>3.6 (1.9–6.7)</td>
</tr>
<tr>
<td>&gt;11</td>
<td>6.7 (3.4–12.9)</td>
</tr>
</tbody>
</table>

*Adjusted for all variables in the model.

### Table 4. Multivariate analyses of human papillomavirus (HPV) type 16 seropositivity in men.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>≥30</td>
<td>1.9 (0.9–4.1)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Residence</td>
<td></td>
</tr>
<tr>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity and residence</td>
<td></td>
</tr>
<tr>
<td>Nonurban non-Hispanic white</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>Nonurban non-Hispanic black</td>
<td>1.7 (0.9–3.0)</td>
</tr>
<tr>
<td>Nonurban Mexican American</td>
<td>1.3 (0.7–2.3)</td>
</tr>
<tr>
<td>Urban non-Hispanic white</td>
<td>2.8 (1.6–5.0)</td>
</tr>
<tr>
<td>Urban non-Hispanic black</td>
<td>2.1 (1.2–3.5)</td>
</tr>
<tr>
<td>Urban Mexican American</td>
<td>1.2 (0.6–2.3)</td>
</tr>
<tr>
<td>Age at first intercourse, years</td>
<td></td>
</tr>
<tr>
<td>≥18</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>&lt;18</td>
<td>2.5 (1.7–4.0)</td>
</tr>
<tr>
<td>History of sex with a man</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>Ever</td>
<td>6.1 (2.7–14.0)</td>
</tr>
<tr>
<td>Sexual activity, years</td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>≥10</td>
<td>3.6 (1.8–7.3)</td>
</tr>
</tbody>
</table>

**NOTE.** CI, confidence interval; —, data not available.

*Adjusted for all variables in the model.

Significant interaction between residence and race/ethnicity precludes reporting of odds ratios for each variable separately.
References


44. Schuster MA, Bell RM, Kanouse DE. The sexual practices of adolescent...


