Prevalence of High-Risk Human Papillomavirus Among Older Women

Stacy Tessler Lindau, MD, MAPP, Melinda L. Drum, PhD, Elyzabeth Gaumer, MA, Hanna Surawska, BA, and Jeanne A. Jordan, PhD

OBJECTIVE: To estimate the prevalence, genotypes, and individual-level correlates of high-risk human papillomavirus (HPV) among women aged 57–85.

METHODS: Community-residing women (N=1,550), aged 57–85, were drawn from a nationally representative probability sample. In-home interviews and biomeasures, including a self-collected vaginal specimen, were obtained between 2005 and 2006. Specimens were analyzed for high-risk HPV DNA using Hybrid Capture 2; of 1,028 specimens provided, 1,010 were adequate for analysis. All samples testing positive were analyzed for HPV DNA by L1 consensus polymerase chain reaction followed by type-specific hybridization.

RESULTS: The overall population-based weighted estimate of high-risk HPV prevalence by Hybrid Capture 2 (Digene Corp.) was 6.0% (95% confidence interval 4.5–7.9). Current marital and smoking status, frequency of sexual activity, history of cancer, and hysterectomy were associated with high-risk HPV positivity. Among high-risk HPV–positive women, 63% had multiple type infections. Human papillomavirus-16 or -18 was present in 17.4% of all high-risk HPV–positive women. The most common high-risk genotypes among high-risk HPV–positive women were HPV-61 (19.1%), -31 (13.1%), -52 (12.9%), -58 (12.5%), -83 (12.3%), -66 (12.0%), -51 (11.7%), -45 (11.2%), -56 (10.3%), -53 (10.2%), -16 (9.7%), and -62 (9.2%). Being married and having an intact uterus were independently associated with lower prevalence of high-risk HPV. Among unmarried women, current sexual activity and smoking were independently and positively associated with high-risk HPV infection.

CONCLUSION: In this nationally representative population, nearly 1 in 16 women aged 57–85 was found to have high-risk HPV, and prevalence was stable across older age groups.

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LEVEL OF EVIDENCE: II

From the University of Chicago Departments of Obstetrics and Gynecology and Medicine–Geriatrics, the University of Chicago Cancer Research Center, and the University of Chicago Center NORC on Aging Core on Biomarkers in Population-Based Aging Research; the University of Chicago Department of Health Studies; the University of Chicago Department of Sociology; the University of Chicago Department of Obstetrics and Gynecology, Chicago, Illinois; and the University of Pittsburgh Department of Pathology, Magee-Women's Research Institute, Pittsburgh, Pennsylvania.

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Corresponding author: Stacy Tessler Lindau, MD, MAPP, The University of Chicago, Departments of Ob/Gyn and Medicine–Geriatrics, 5841 South Maryland Avenue, MC2050, Suite R311, Chicago, IL 60637; e-mail: slindau@uchicago.edu.

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Nearly all cases of cervical intraepithelial neoplasia and cancer are attributable to sexually transmitted genital tract infection with one or more of approximately 15 oncogenic, or high-risk, types of human papillomavirus (HPV).[1,2] In the United States, 20% of cervical-cancer cases, but 36% of cervical-cancer deaths, occur in women age 65 and older.[3] Annual direct medical costs for preventing and treating HPV-related anogenital disease across the whole U.S. population are estimated to exceed $4 billion; morbidity and cost among older women have not been quantified.[4]

The natural history of genital-tract HPV in older women is poorly understood. A bimodal age distribution in HPV prevalence has been observed in some populations.[5–8] The second peak in HPV prevalence

in older women, where observed, is thought to result primarily from persistent infection.[9] High-risk types may be more likely than low-risk types to persist.[10,11] Susceptibility to and failure to clear genital HPV infection may be affected by immune function, sex-hormone status, or vaginal epithelial function.[9]

Women age 65 and older will comprise 14.8% of the U.S. population by 2010 and 21.7% by 2030.[12] Many older women are sexually active[13] and engage in other behaviors, such as smoking,[14] that are known risk factors for genital-tract HPV in younger women. Older women initiating new sexual relationships in later life may be exposed to HPV strains for the first time.[15] Substantially more women are aging with the uterus intact[16] and, therefore, remain vulnerable to cervical HPV disease and Pap test abnormalities. Public health messages and commercial advertising about cervical cancer screening, genital HPV, and the HPV vaccine reach women (and men) of all ages and generate public concern about vulnerability to infection, transmission, and sequelae.[17] The age-group–specific population prevalence of high-risk HPV among older women in the United States and its consequences for older women's health are unknown.

This study aims to extend recent HPV-prevalence data[18] by estimating the prevalence, genotypes, and individual-level correlates of high-risk HPV among women age 57–85.

MATERIALS AND METHODS

A nationally representative probability sample of community-dwelling adults aged 57–85 was generated from U.S. households screened in 2004 for the Health and Retirement Study, which was seeking participants age 56 and younger. Of 4,017 eligible participants, 3,005 (1,455 men, 1,550 women) were interviewed between July 2005 and March 2006, yielding a weighted response rate of 75.5% (unweighted 74.8%). In-home interviews conducted by trained female field staff (unless the respondent requested a man) included an interviewer-administered, standardized, computer-assisted questionnaire and biological measures. A detailed description of the National Social Life, Health and Aging Project study population and study design has been published previously.[13]

All women selected for participation in the National Social Life, Health and Aging Project were eligible for this study. Of 1,550 eligible women, 1,028 (66.3% unweighted, 67.5% weighted) agreed to submit a self-administered vaginal swab specimen (Fig. 1). Of these, nine respondents tried but were unable to collect the vaginal swab, equipment problems occurred in the collection of six swabs, two specimens were lost in transit, and one specimen was missing in error. Thus, 1,010 (98.0%, 66.2% overall, weighted) specimens were adequate for analysis.

Nonresponders to the vaginal swab protocol were significantly more likely than responders to be older (older than 75 years), have less than a high school education (Table 1), and were less likely to report a recent pelvic examination, menopausal prescription hormone use, or frequent sexual activity in the previous year. A physical or health problem was the most common recorded reason for not submitting a vaginal specimen. The protocol was approved by the University of Chicago and the NORC Institutional Review Boards; all respondents gave written informed consent.

Race and ethnicity were self-reported. Sex was defined as "any mutually voluntary activity with another person that involves sexual contact, whether or not intercourse or orgasm occurs." For those reporting a current (prior 12 months) sexual partner, sexual frequency, condom use, and partner's sex were collected for up to the two most recent partners. Partner infidelity (known or perceived) was collected for up to the two most recent partners for a randomly selected two thirds of survey respondents. Questions about sexual activity were refused by 2–7% of respondents. Data regarding the most recent sexual partner are used in the analyses reported here.

Smoking was assessed using questions adapted from a major epidemiologic study of aging.[19] Physical health was self-rated using the standard 5-point scale, and comorbidities were assessed using a modified Charlson Index.[20] Current medications were logged and classified according to the Multum Drug Database: Lexicon Plus version (Cerner Multum, Denver, CO).[21] Other health and health-behavior variables were obtained by self-report.

Women were given an illustrated instruction card with collection materials[22] and directed to a bathroom or other private room. The swab for HPV testing was secured inside a labeled tube containing 1 mL Specimen Transport Medium (Digene Corp., Gaithersburg, MD). Tubes were stored on wet ice until day's end and shipped overnight on cold packs to the University of Pittsburgh, Magee-Women's Hospital Department of Pathology clinical microbiology laboratory of J.A.J.

High-risk HPV–DNA testing was performed using the Hybrid Capture 2 High-Risk HPV DNA Test™ (Catalog No. 5199-1220; Digene Corp.) according to the manufacturer's protocol. The high-risk Hybrid Capture 2 signal amplification assay contains a cocktail of probes

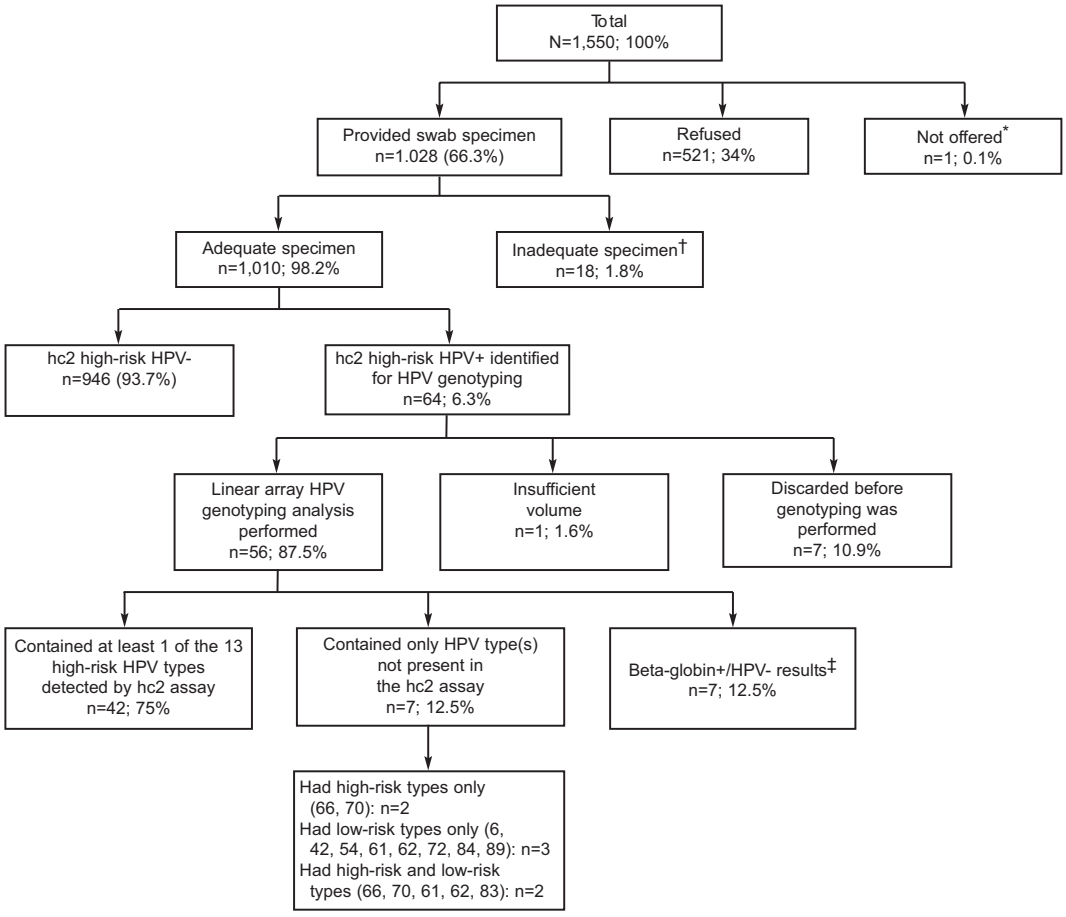

Fig. 1. National Social Life, Health and Aging Project human papillomavirus (HPV) study participation and test results summary (n, unweighted percentages). hc2, Hybrid Capture 2 (Digene Corp.). *Owing to computer entry error for respondent sex, this respondent was not offered vaginal swab testing. †Tried, but unable to provide specimen (n=9), equipment/material problems (n=6), lost/ruined (n=3). ‡Negative for all 37 anogenital high-risk and low-risk HPV genotypes detectable by the Linear Array assay.

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complementary to 13 high-risk HPV types (HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, and -68). In addition to the kit controls, an external sample-processing control for adequate cells lysis (HeLa cells, which contain integrated HPV-18 DNA) was processed with each batch of specimens. Specimens with relative light unit/cutoff values of 1.0 or more, obtained using the Digene Microplate Luminometer 2000 Instrument (Digene Corp.), were considered positive for high-risk HPV DNA.

Genotyping was performed on 56 Hybrid Capture 2 high-risk HPV–positive specimens (Fig. 1) using the Linear Array HPV Genotyping Test (research use only) and Linear Array Detection Kit (Roche Molecular Systems Inc., Pleasanton, CA). Only Hybrid Capture 2 high-risk HPV–positive specimens were genotyped for this study. The denatured specimens were stored at −20°C before being thawed, neutralized, and genotyped. For compatibility with the QIAamp® MinElute Media Kit protocol for DNA extraction (Cat. No. 57704, QIAGEN, Valencia, CA), 250 microliters of each denatured Specimen Transport Medium (Digene Corp.) was re-acidified to a pH just below 7.0 and the entire volume extracted. Fifty microliters of the final 120 microliters extract volume were amplified by polymerase chain reaction (PCR) in a master mix containing hot-start *Taq* polymerase and biotin-labeled PGMY09/11 primer set to amplify 37 different anogenital HPV genotypes (450 base pair target) along with a primer set to human β-globin (268 base pair target), which served as an internal control for DNA amplification. Thermocycling was performed using the Gold-plated 96-Well GeneAmp PCR System 9700 (part no. 4314878; Applied Biosystems, Foster City, CA) thermocycler. Amplicon denaturation and detection was carried out using the Linear Array Detec-

Table 1. Demographic Characteristics of Vaginal Swab Specimen Responders (n=1,028*) and Nonresponders (n=521*)

	Responders, % (95% CI)†	Nonresponders, % (95% CI)†
Overall (age 57–85 y)	67.6 (63.6–71.2)	32.4 (28.8–36.4)
Age group, y		$P<.001$‡
57–64	41.0 (37.6–44.6)	35.2 (30.3–40.5)
65–74	36.4 (33.1–39.8)	31.4 (26.6–36.7)
75–85	22.6 (20.2–25.2)	33.3 (28.6–38.5)
Race/ethnicity§		$P=.86$‡
Non-Hispanic white	80.4 (75.1–84.7)	80.8 (75.0–85.6)
Non-Hispanic black	10.6 (7.8–14.3)	11.3 (7.8–16.2)
Hispanic	7.1 (3.8–12.9)	5.7 (3.5–9.4)
Other	1.9 (0.9–3.7)	2.1 (1.1–4.1)
Current marital status		$P=.29$‡
Married	56.4 (53.3–59.5)	53.7 (47.6–59.6)
Living with partner	2.5 (1.5–4.4)	1.8 (0.7–4.4)
Widowed	23.5 (20.5–26.8)	28.4 (23.9–33.4)
Separated	1.3 (0.8–2.1)	0.6 (0.2–1.6)
Divorced	13.2 (11.3–15.4)	11.3 (7.8–16.0)
Never married	3.0 (2.1–4.3)	4.3 (2.7–6.8)
Education		$P=.02$‡
Less than high school	17.7 (14.3–21.7)	25.3 (20.3–31.2)
High school or equivalent	29.6 (26.2–33.2)	29.4 (24.9–34.3)
Some college/associate's degree	34.9 (30.7–39.4)	27.4 (22.4–33.0)
Bachelor's degree or higher	17.8 (14.6–21.6)	18.0 (13.6–23.4)
Insurance status		$P=.41$‡
Medicare	63.5 (59.1–67.7)	64.9 (59.0–70.5)
Private without medicare	32.1 (27.8–36.7)	29.4 (23.7–35.7)
VA, medicaid, other	3.7 (2.5–5.5)	4.1 (2.2–7.4)
No insurance	0.7 (0.4–1.5)	1.6 (0.7–4.0)

CI, confidence interval.
* Unweighted frequencies.
† Estimates are weighted to account for differential probabilities of selection and differential nonresponse.
‡ *P* value represents global test of significance.
§ Race and ethnicity were self-reported using the questions, "Do you consider yourself primarily white or Caucasian, black or African-American, American Indian, Asian, or something else?" and "Do you consider yourself Hispanic or Latino?"

tion Kit (Roche Molecular Systems Inc.). For each specimen to be considered valid, both the high- and low-level β-globin controls had to yield a visible band on the blot. For each run to be considered valid, both positive and negative controls had to perform as expected. The ambiguous XR/52 probe data were handled as follows: HPV type 52 was considered positive only when the HPV GT52/33/35/58 band alone was visible. Although coinfection with HPV type 52 cannot be ruled out in cases where both the HPV GT52/33/35/58 band and one or more of the individual GT33, GT35, and/or GT58 bands were visible, we interpreted those specimens as negative for HPV type 52. To ensure reproducibility, 22 of the 56 specimens were randomly selected and retested. Without exception, the number of bands and their relative staining intensities were similar between runs.

The analytic sample consisted of 1,010 responders who provided an adequate vaginal self-swab specimen. High-risk HPV prevalence (at least one high-risk genotype present by Hybrid Capture 2) was estimated with 95% confidence interval (CI) obtained using a logit transform to ensure that the confidence limit would fall between 0 and 1. Logistic regression was used to model associations between high-risk HPV and individual factors. All analyses accounted for the survey sampling design through incorporation of sampling strata and clusters as well as weights that adjusted for differential probability of selection and differential nonresponse. Standard errors were computed using the Taylor linearization method.[23] Estimates in tables are marked if the variance estimate is based on fewer than 12 strata with observations in both primary sampling units, following guidelines for the National Health and Nutrition Examination Survey.[24] Results were not adjusted for multiple testing. A sensitivity analysis was conducted in which all analyses were repeated, with missing high-risk HPV values recoded as high-risk HPV–negative (n=539, Fig. 1). Analyses were conducted using Stata Statistical Software 10 (StataCorp, College Station, TX).

Before analysis, independent variables measured on a continuous scale or as counts were categorized because of linearity assumptions underlying the use of continuous covariates. Lifetime number of sex partners was categorized as zero, one, or two or more. Age was categorized as 57–64, 65–74, and 75–85 years for consistency with previous studies[25] and the age structure of the National Social Life, Health and Aging Project sample. Duration since last menstrual period was broken into decades, and then decades were collapsed as indicated by model fit using the criteria described below. Categories were collapsed before analysis if necessary to obtain adequate numbers of observations and cases within each category. During analysis, categories that did not differ significantly and had similar odds ratios (ORs) were collapsed, provided that the collapsed categories were clinically meaningful. Univariable results are reported with minimal collapsing. Selected clinically relevant interactions were tested: between married and each of the sexual behavior variables (lifetime number of sex partners, sex in the previous year, condom use) and between duration since last menstrual period and hysterectomy.

Multivariable logistic models were fit to identify independent correlates of high-risk HPV. Terms considered for inclusion were the significant interaction of marital status (married compared with not married) and sex in the previous year, factors significant at $P<.20$ in univariable analysis, and potential confounders (age, lifetime number of sex partners). Model selection was conducted using a stepwise approach, keeping within the limitations of the number of high-risk HPV cases.[26] Terms were retained if significant at $P\leq.05$ or if they modified the effect of a significant covariate. Multivariable analysis was conducted for the entire sample and for women not currently married; multivariable analysis among married women was precluded by the small number of high-risk HPV cases (n=19).

RESULTS

The mean age of respondents was 68 years, mean age at menopause was 46 years, mean duration since menopause was 22 years, mean lifetime number of sex partners was 4.5 (median 2.0), and mean number of pregnancies was 2.8. The population prevalence of high-risk HPV was estimated to be 6.0% (95% CI 4.5–7.9). This corresponds to 1.8 (95% CI 1.4–2.4) million women aged 57–85 with prevalent high-risk HPV infection, using 2006 Census estimates.[27]

High-risk HPV prevalence was estimated according to sociodemographic characteristics (Table 2). Prevalence of high-risk HPV infection did not differ significantly by age group, race/ethnicity, education, or insurance status. Current marital status was a strong, significant predictor of high-risk HPV infection. Prevalence was lowest among those currently married and was highest among those who were divorced.

The frequencies of HPV genotypes were determined for 56 of the 64 high-risk Hybrid Capture 2-positive specimens (Fig. 1). Figure 2 illustrates their distribution (2A) and copresence (2B). One or more of the four genotypes included in the quadrivalent HPV vaccine, -6, -11, -16, -18 was detected in 27.2% of women with high-risk HPV, although zero cases of HPV-11 were found. Nearly two thirds (63%) of women with high-risk HPV had multiple types detected. Among 49 specimens with any high-risk HPV genotype detected, 37 contained two or more genotypes. The most common high-risk genotypes found among high-risk HPV–positive women were HPV-61 (19.1%), -31 (13.1%), -52 (12.9%), -58 (12.5%), -83 (12.3%), -66 (12.0%), -51 (11.7%), -45 (11.2%), -56 (10.3%), -53 (10.2%), -16 (9.7%), and -62 (9.2%). No specimens tested positive for both high-risk HPV-16 and -18; HPV-16 or -18 was present in 17.4% of all high-risk HPV–positive women. These genotype prevalences may be underestimates of the prevalences in the entire population because genotyping was limited to women who first tested positive for high-risk HPV by Hybrid Capture 2.

Behavioral and health factors significantly associated with higher high-risk HPV prevalence in bivariate analyses included current smoking, cancer, and hysterectomy. Although data on prior chemotherapy use were unavailable, 47 women (4.6% of high-risk HPV–negative and 12.6% of high-risk HPV–positive) were currently using an antineoplastic agent. High-risk HPV was positively associated with current chemotherapy use (OR 2.99, 95% CI 1.17–7.68, $P=.02$). High-risk HPV prevalence also was associated with sex in the prior 12 months, but the nature of the association differed between married and unmarried women (Table 3).

High-risk HPV prevalence was significantly higher among women who reported two or more sexual partners over their lifetime compared with those who reported one or none (OR 2.54, 95% CI 1.07–6.02, $P=.04$). Only three women (one Hybrid Capture 2-negative, two Hybrid Capture 2-positive) reported having more than one current sexual partner. Very few women reported condom use: 1.5% (95% CI 0.9–2.6) overall and 3.4% (95% CI 1.96–5.98) of sexually active women. Likewise, very few women reported ever being diagnosed with cervical

Table 2. Estimated High-Risk Human Papillomavirus Prevalence Using Digene Hybrid Capture 2 Assay by Demographic Characteristics

	n*	High-risk HPV Prevalence, % (95% CI)†	OR (95% CI)
Overall (age 57–85 y)	1,010	6.0 (4.5–7.9)	–
Age group, y‡			*P*=.73§
57–64	332	5.8 (3.4–9.8)	1.00 [referent]
65–74	376	6.8 (4.3–10.6)	1.19 (0.53–2.68)
75–85	302	5.0 (2.6–9.4)	0.85 (0.36–2.02)
Race/ethnicity‖			*P*=.13§
Non-hispanic white	693	6.1 (4.5–8.4)	1.00 [referent]
Non-hispanic black	187	8.4 (4.0–16.7)	1.43 (0.62–3.29)
Hispanic	108	2.6 (1.1–6.2)**	0.42 (0.16–1.16)
Current marital status¶			*P*<.0001§
Married	483	3.6 (2.3–5.7)	1.00 [referent]
Widowed	318	6.1 (3.7–9.9)	1.75 (0.90–3.39)
Divorced	132	13.6 (9.2–19.7)	4.22 (2.38–7.49)
Never married	34	9.7 (3.1–26.5)**	2.88 (0.79–10.6)
Education			*P*=.67§
Less than high school	233	7.5 (4.0–13.8)	1.00 [referent]
High school or equivalent	280	4.7 (2.7–8.0)	0.61 (0.26–1.40)
Some college/associate's degree	328	5.8 (3.4–9.6)	0.75 (0.29–1.93)
Bachelor's degree or higher	169	7.0 (3.4–14.0)	0.92 (0.33–2.56)
Insurance status#			*P*=.70§
Medicare	572	5.3 (3.7–7.5)	1.00 [referent]
Private without medicare	226	5.8 (3.2–10.6)	1.12 (0.51–2.43)
VA, medicaid, other	35	9.4 (2.3–31.5)**	1.87 (0.40–8.72)

HPV, human papillomavirus; CI, confidence interval; OR, odds ratio.

* Unweighted frequencies.

† Estimates are weighted to account for differential probabilities of selection and differential nonresponse. The unweighted total number of high-risk HPV cases was 64. A double asterisk (**) indicates that the variance estimate is based on fewer than 12 strata with observations in both primary sampling units.

‡ High-risk HPV prevalence also did not differ by age considered as a continuous covariate or categorized into 5-year intervals. Polynomial terms (age squared, age cubed) were tested and were nonsignificant.

§ *P* value represents global test of significance.

‖ Excluding "other" race (n=18, no cases). Race and ethnicity were self-reported using the questions, "Do you consider yourself primarily white or Caucasian, black or African-American, American Indian, Asian, or something else?" and "Do you consider yourself Hispanic or Latino?"

¶ Excluding "separated" (n=22) and "nonmarital cohabiting relationship" (n=21) owing to small sample size.

Excluding "no insurance" (n=8, no cases).

cancer (1.4%, 95% CI 0.7–2.7), a sexually transmitted infection (STI) other than HPV (11%, 95% CI 9.1–13.9), or genital warts (2%, 95% CI 1.0–3.6). High-risk HPV was detected in 4.4% of women who reported never having had sex.

High-risk HPV prevalence was significantly associated with having had sex in the prior 12 months only among unmarried (including formerly married) women (Table 3), corresponding to a significant interaction of marital status with sex in this time period (*P*=.03). Among married women, high-risk HPV prevalence did not differ significantly between no sex and infrequent sex in the prior 12 months, whereas more frequent sex (more than once a month) was significantly associated with a decreased prevalence of high-risk HPV (OR 0.12, 95% CI 0.03–0.45, *P*=.002). Spousal infidelity was reported by 5.9% of married women and was significantly associated with having high-risk HPV (OR 5.39, 95% CI 1.43–20.4, *P*=.01). Too few cases of HPV (n=12) occurred among unmarried women who reported sex within the previous year to further evaluate the effect of frequency of sex in this subgroup. Owing to heterogeneity and sparse data on the timing and nature of the relationship with the most recent sexual partner among unmarried women, the effects of partner infidelity in this subgroup were not explored.

The prevalence of hysterectomy, which was significantly associated with higher high-risk HPV prevalence, was 46% (95% CI 41.9–49.2). Women who had a hysterectomy did not differ from those who did not with respect to sexual behavior, current smoking, demographic characteristics, history of cervical dysplasia, or number of pregnancies. Hysterectomy was significantly associated with poorer self-rated health (very poor, poor compared with higher

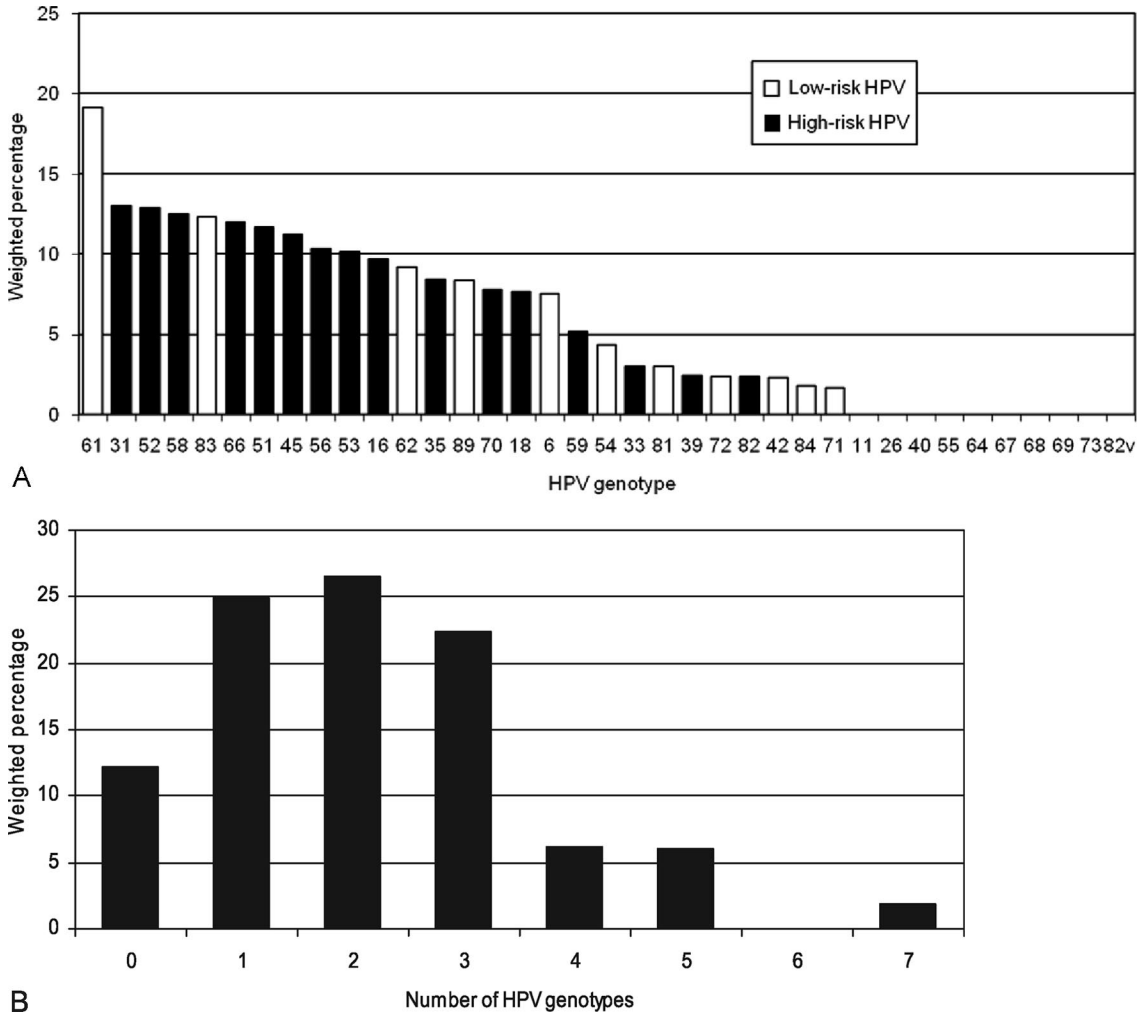

Fig. 2. A. Human papillomavirus (HPV) genotype distribution among 56 Hybrid Capture 2 high-risk HPV-positive specimens. **B.** Number of HPV genotypes present among 56 Hybrid Capture 2 high-risk HPV-positive specimens. Note: Weighted percentages underestimate population prevalences because high-risk HPV–negative women were not genotyped. Standard errors are not shown because they are based on fewer than eight variance strata with observations in both primary sampling units.
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rating: OR 1.73, 95% CI 1.18–2.52). Among women reporting premenopausal hysterectomy, high-risk HPV prevalence did not differ between those with bilateral oophorectomy and those with at least one remaining ovary (P=.46). Among women who did not have a hysterectomy, the likelihood of high-risk HPV presence was significantly higher if more than 20 years had elapsed since the last menstrual period (age-adjusted OR 9.25, 95% CI 2.63–32.5, P=.001).

In multivariable analysis, marital status and hysterectomy were independent correlates of high-risk HPV detection, adjusted for age (Table 4). Among unmarried women, higher high-risk HPV prevalence was independently associated with sex in the prior 12 months and current smoking, adjusted for age and lifetime number of sex partners. Although the number of cases of high-risk HPV among married women was too small to conduct a full multivariable analysis, the association of more frequent sex with lower high-risk HPV remained after adjustment for age and lifetime number of sex partners.

In the sensitivity analysis, in which 539 missing high-risk HPV values were recoded as high-risk HPV–negative, the overall prevalence of high-risk HPV was 4.0% (95% CI 3.0–5.2). The associations between high-risk HPV and respondent characteristics were similar.

Table 3. Estimated High-Risk Human Papillomavirus Prevalence Using Digene Hybrid Capture 2 Assay by Behavioral and Health Characteristics

	n*	High-risk HPV Prevalence, % (95% CI)†	OR (95% CI)†
Sexual behavior			
Lifetime number of sex partners			*P*=.10‡
0	87	4.4 (1.3–13.8)	1.00 [referent]
1	300	2.8 (1.2–6.5)	0.63 (0.15–2.73)
2 or more	542	7.7 (5.6–10.6)	1.81 (0.50–6.64)
Sex within the previous 12 mo			
Among married			*P*=.49
No	159	4.7 (2.4–9.2)	1.00 [referent]
Yes	313	3.2 (1.5–6.6)	0.67 (0.21–2.13)
Among unmarried			*P*=.01
No	466	6.8 (4.4–10.3)	1.00 [referent]
Yes	57	23.7 (11.6–42.5)**	4.29 (1.47–12.5)
Health behavior			
Current self-reported smoking status			*P*=.04
Nonsmoker, including former smoker	874	5.5 (4.0–7.5)	1.00 [referent]
Current smoker	136	9.1 (5.9–13.8)	1.73 (1.03–2.91)
Last Pap test			*P*=.72‡
Within the past y	408	5.0 (3.0–8.1)	1.00 [referent]
Between 1 and 5 y ago	353	6.6 (4.2–10.3)	1.35 (0.64–2.83)
More than 5 y ago§	192	5.7 (3.3–9.9)	1.17 (0.52–2.65)
Last pelvic examination			*P*=.45‡
Within the past y	413	4.8 (2.8–8.0)	1.00 [referent]
Between 1 and 5 y ago	357	7.1 (4.5–11.1)	1.53 (0.69–3.38)
More than 5 y ago‖	176	5.2 (3.0–8.9)	1.09 (0.47–2.57)
Health characteristics			
Self-rated physical health			*P*=.54
Fair to excellent	934	5.9 (4.4–7.9)	1.00 [referent]
Poor	71	8.1 (2.9–20.7)**	1.42 (0.45–4.44)
Comorbidities			*P*=.19‡
0–1	523	5.0 (3.2–7.7)	1.00 [referent]
2	244	6.0 (3.6–9.9)	1.23 (0.59–2.57)
3–9	243	8.6 (5.4–13.6)	1.80 (0.95–3.40)
Cervical dysplasia			*P*=.95
No	850	5.7 (4.2–7.8)	1.00 [referent]
Yes	75	5.9 (2.2–14.9)	1.03 (0.34–3.16)
Any cancer			*P*=.04
No	886	5.2 (3.8–7.3)	1.00 [referent]
Yes	124	11.5 (6.1–20.8)	2.35 (1.05–5.28)
Total number of pregnancies			*P*=.90‡
0	66	8.1 (2.8–21.0)	1.00 [referent]
1	81	4.4 (1.3–13.6)	0.52 (0.10–2.85)
2	197	6.8 (3.9–11.4)	0.83 (0.25–2.69)
3	218	6.3 (3.2–12.1)	0.76 (0.21–2.84)
4 or more	447	5.3 (3.4–8.2)	0.64 (0.21–1.96)
Hysterectomy¶			*P*=.02‡
Never	553	3.5 (2.2–5.5)	1.00 [referent]
After menopause	91	9.3 (3.8–21.2)	2.82 (0.91–8.70)
Before menopause	359	8.8 (5.8–13.3)	2.66 (1.34–5.30)
Duration since last menstrual period, y			*P*=.13‡
Less than 10	114	2.3 (0.7–7.7)	1.00 [referent]
10–19	230	4.0 (1.9–8.2)	1.77 (0.43–7.33)
20–29	313	9.6 (6.3–14.6)	4.52 (1.18–17.3)
30–39	194	6.9 (3.9–11.9)	3.16 (0.79–12.6)
40–63	71	7.7 (2.2–23.8)**	3.51 (0.36–34.3)

(continued)

Table 3. Estimated High-Risk Human Papillomavirus Prevalence Using Digene Hybrid Capture 2 Assay by Behavioral and Health Characteristics (*continued*)

	n*	High-risk HPV Prevalence, % (95% CI)†	OR (95% CI)†
Prescription hormone use since menopause			*P*=.99
No	532	6.0 (4.2–8.5)	1.00 [referent]
Yes	475	6.0 (4.1–8.8)	1.00 (0.60–1.67)

HPV, human papillomavirus; CI, confidence interval; OR, odds ratio.
* Unweighted frequencies.
† Estimates are weighted to account for differential probabilities of selection and differential nonresponse. The unweighted total number of high-risk HPV cases was 64. A double asterisk (**) indicates that the variance estimate is based on fewer than 12 strata with observations in both primary sampling units.
‡ *P* value represents global test of significance.
§ Includes 20 women who reported never having a Pap test.
‖ Includes 33 women who reported never having a pelvic examination.
¶ Includes total and supracervical hysterectomy.

DISCUSSION

Prevalence of high-risk HPV DNA in a representative sample of U.S. women aged 57–85 was 6.0%, corresponding with 1.8 (95% CI 1.4 to 2.4) million women, and was stable across older age subgroups. Risk factors in younger women are also significant correlates of high-risk HPV presence in older women. Only about one in 30 sexually active older women uses condoms. Additional health-related correlates of high-risk HPV positivity, not appreciated in younger populations, are identified. Among older women with genital high-risk HPV, the vast majority exhibit multiple genotype infection.

Table 4. Multivariate Analysis of Factors Associated with High-Risk Human Papillomavirus Positivity Among Women Aged 57–85

	OR (95% CI)*	*P*
All women†		
Married		.001
No	1.00 [referent]	
Yes	0.38 (0.22–0.66)	
Hysterectomy		.01
No	1.00 [referent]	
Yes	2.63 (1.37–5.04)	
Unmarried women‡§		
Sex within the last 12 mo		.02
No	1.00 [referent]	
Yes	3.94 (1.23–12.6)	
Current smoker		.01
No	1.00 [referent]	
Yes	3.54 (1.39–8.98)	

CI, confidence interval; OR, odds ratio.
* Estimates are weighted to account for differential probabilities of selection and differential nonresponse.
† Estimates are adjusted for age. Candidate covariates also included race and ethnicity, smoking status, any cancer, number of comorbidities, lifetime number of sex partners, sex within the last 12 months, and the interaction of married and sex within the last 12 months. The unweighted total number of high-risk human papillomavirus (HPV) cases was 64.
‡ Estimates are adjusted for age and lifetime number of sex partners. Candidate covariates also included race and ethnicity, hysterectomy, any cancer, and number of comorbidities. The unweighted total number of high-risk HPV cases among unmarried women was 45.
§ The number of cases of HPV among married women (n=19) was insufficient to fit a multivariate model.

Estimated high-risk HPV prevalence for women aged 57–85 is nearly identical to that reported by the U.S. National Health and Nutrition Examination Survey for women aged 50–59, using comparable methods.[18] In a validation study including older women, high agreement was found (88.1%, κ=0.73) between physician and self-swab specimens for detecting HPV.[28] The frequency of oncogenic HPV types 16 and 18 translates roughly to minimum population prevalences of 0.5% and 0.4%, respectively; no individual tested positive for both HPV types 16 and 18. These findings are very similar to the U.S. National Health and Nutrition Examination Survey prevalence estimates for these genotypes among females age 14–59, including the rare copresence of types 16 and 18 (0.1%).[18]

Other U.S.-based studies of HPV that include older women are limited by relatively small, clinical convenience samples and aggregation of women age 60 and older. Age-standardized estimates of high-risk HPV in 1,154 female patients age 16 and older between 1989 and 1990 were 4.2–4.9% using a PCR and DNA hybridization assay.[29] A smaller study of 260 healthy, postmenopausal women seeking gynecologic care during the period from 1997–1999 found a high-risk HPV prevalence of 6%[30] using similar methods.

The frequency of multiple type infection found here is significantly higher than that observed among younger women with any genital HPV[18] or high-risk HPV specifically.[31] This may reflect cumulative lifetime exposure,[32] an association between multiple type

infection and vulnerability to persistence[33] or reactivation of latent infection,[34] and/or a senescence-related reduction in capacity to suppress dormant virus or clear new infection.[35] Longitudinal, population-based data are needed to elucidate mechanisms underlying the natural history of oncogenic HPV in older women. The implications of long-term carriage of genital tract HPV well beyond menopause are not well understood; further work is needed to appreciate the implications in older women for vulvovaginal diseases, transmission to partners, Pap test abnormalities, treatment decisions about gynecologic comorbidities, and psychological well-being.

The prevalence of high-risk HPV is higher in hysterectomized compared with nonhysterectomized women, despite similar sexual behavior. Understanding the role of hysterectomy in the natural history of high-risk HPV is complex, limited in this study by self-report, and should incorporate factors such as timing and type of hysterectomy, oophorectomy, indication for hysterectomy, and adjunctive treatment. In two studies, Castle et al documented high-risk HPV in younger women who had undergone hysterectomy but found no difference in HPV prevalence by hysterectomy status.[29,36] One study suggests that persistent genital tract HPV infection in older women may be a marker of immune compromise.[35] This may partially explain the relationship we find between hysterectomy and high-risk HPV. We found that a history of any cancer, a higher number of cancers, and any current antineoplastic agent use were associated with a higher prevalence of high-risk HPV and that women with hysterectomy were less healthy than women who did not have hysterectomy.

There were limitations to our study. Cervical dysplasia and sexually transmitted infection history are likely underreported,[37] thereby attenuating expected associations with HPV. Sexuality data also were self-reported; prior work with this data set demonstrates high internal and external validity and low item nonresponse using valid interview methods.[13,38] Differences between vaginal swab nonresponders and responders could bias prevalence estimates; however, in the extreme case where all nonresponders are assumed to be high-risk HPV negative, overall prevalence is still 4.0% (2.9% in the women aged 75–85) and the same correlates are identified. In some subgroups, the very small number of participants with high-risk HPV results in wide CIs, which have been reported for completeness but should be regarded with caution. Use of the self-collected specimens may lead to detection of different HPV types than those collected by direct endocervical sampling and may favor detection of low-risk types with predilection for the vagina.[18,28] The degree of vaginal atrophy also may influence HPV detection,[25] as suggested in our study by a higher rate of detection in women with a longer duration since last menses. Also, collecting a vaginal specimen from a single time point does not distinguish between new, persistent, or reactivated latent infection. Furthermore, because the Hybrid Capture 2 assay does not control for cellular adequacy, a small but unknown proportion may have been falsely negative.

High-risk HPV prevalence was stable across older age groups and nearly equivalent to that estimated by the U.S. National Health and Nutrition Examination Survey for women in the sixth decade. Among older women with high-risk HPV positivity, the proportion of HPV types targeted by the HPV vaccine was 27.2% (95% CI 14.4–36.9), comparable with 1.2% (95% CI 0.8–2.0) prevalence. Although an underestimate of the prevalence of vaccine types among all older women, this is in contrast to the estimated 3.4% prevalence among the general population of females age 14–59.[18] These data provide physicians and the public new information pertinent to HPV counseling, screening decisions, and health-related quality of life.[39]

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