THE CORRELATION BETWEEN HPV POSITIVITY AND ABNORMAL CERVICAL CYTOLOGY DIFFERS BY AGE AMONG PERIMENOPAUSAL WOMEN

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Abstract

Objectives—We explored the age-stratified correlates and correlations between HR-HPV infection and cervical abnormalities in perimenopausal women.

Materials and methods—HPV testing and Pap smear screening were performed at baseline on 841 routinely screened women age 35–60 years in the HPV in Perimenopause (HIP) cohort. Demographic, behavioral and medical information was collected through telephone administered questionnaires. Descriptive analyses were used to examine the correlation between HR-HPV infection and cervical abnormalities by age. Logistic regression was used to determine correlates of HPV and abnormalities in women under and over 45 years of age.

Results—The prevalence of HPV, HR-HPV and cervical abnormalities decreased significantly with increasing age, as did the correlation between HR-HPV and cervical abnormalities. The prevalence of HR-HPV was 50% among younger women with abnormalities but this decreased steadily to 20% HR-HPV detection among 50–54 year old, and no abnormalities were detected in 55–60 year old women. Different correlates of HR-HPV infection and abnormalities were observed in women ≥ 45 years, a pattern not seen in the younger women.

Conclusions—Although the relative proportion of low and high-grade abnormalities did not change with age, we saw a loss of concordance between HR-HPV detection and cytological

abnormalities with increasing age. Current guidelines for cervical cancer screening group together all women age 30 and above. Our data raise important questions about the interpretation of HPV and Pap test results in this age group and suggest that ongoing surveillance of HPV and cytology in cervical cancer screening programs consider a third age stratification among older women.

Keywords

perimenopausal women; menopause; human papillomavirus; HPV; cervical lesions; cytology; cervical cancer; screening; guidelines

INTRODUCTION

Annual screening with cervical Pap smears has dramatically reduced morbidity and mortality due to cervical cancer in the United States in the past 40 years (1). Current consensus guidelines from the American Society for Colposcopy and Cervical Pathology (ASCCP) and the American College of Obstetricians and Gynecologists (ACOG) recommend that HR-HPV testing can be performed in addition to routine cytology screening in women 30 years and older (2, 3). Current guidelines stratify their recommendations at age 30 years because women under 30 are at very low risk of invasive cervical cancer but have a very high probability of prevalent, but transient, HPV infection (4–7). On the other hand, the prevalence of HPV among women 30 years and older is lower than among younger women, resulting in a substantial improvement in the specificity of HPV DNA testing when screening older women.

Although there is an obvious justification for age stratification at 30 years when making recommendations for use of HPV DNA testing in screening, it is unclear whether the guidelines for women over 30 are equally applicable throughout a woman's screening lifetime. Because the rate of pre-neoplastic disease is low (8), few studies of women over age 30 have the power to further stratify by age in order to better inform guidelines. Recently, the ATHENA trial, which included data on over 35,000 women age 30 years and older, reported a decrease in HR-HPV detection with increasing age among women with all grades of pathology-confirmed cervical intraepithelial neoplasia (CIN), with the most striking decrease observed for HPV 16 infection (9). In the HPV in Perimenopause (HIP) cohort of routinely screened women age 35–60 years, we observed a similar trend of decreasing correlation between HR-HPV detection and cervical abnormalities with increasing age While the HIP cohort is small in size relative to the large studies of screening populations (9, 10), it is unique in that we are able to use the extensive personal, behavioral and medical information collected in the HIP study to explore age-stratified patterns and correlates of HPV infection and abnormal cervical cytology in perimenopausal women. Therefore, in this secondary analysis of the HIP study cohort we aimed to further explore the association between any-HPV and HR-HPV detection and abnormal cytology by age.

METHODS

Study population and data collection

Women attending outpatient OB/GYN clinics for routine examination in and around Baltimore, MD from March, 2008 to March, 2011 were recruited to participate in an ongoing prospective cohort study on the natural history of HPV infection through the perimenopausal transition. Women were eligible to participate if they were aged 35–60 years, had an intact cervix, and were willing to provide informed consent. Women were not eligible for enrollment if they were pregnant, had plans to become pregnant, had a history of organ transplantation or were known to be HIV-positive.

After providing informed consent, women completed a baseline questionnaire and gynecological examination. Information on sociodemographic characteristics, reproductive and menstrual history, hormonal and non-hormonal medication use, lifetime sexual history and current sexual behavior were collected using a telephone-administered questionnaire. Data on women's cervical screening and treatment history were also collected, including whether they had obtained previous Pap or HPV tests, had a previous Pap abnormality, and had ever had a colposcopy or treatment for cervical abnormalities. A trained study physician conducted a speculum exam to collect a cervical brush for HPV DNA testing (Digene HPV sampler, Digene, Gaithersburg, MD, USA) as part of the standardized study protocol. Cervical brushes were placed in standard transport medium at 4° for less than 24 hours before being vortexed and stored at −80 °C. All study procedures were approved by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board.

Detection of cervical abnormalities and HPV infection

Women provided signed consent to allow retrieval of their Pap results from the clinical cytopathology labs. The result of the Pap test that was associated with study enrollment was abstracted from the cytopathology report onto a standardized case report form. If the enrollment visit coincided with an annual exam where a Pap test was indicated by clinic protocol, the clinician collected a liquid-based cytology specimen prior to collecting the study samples. Pap results were managed according to standard clinical practice. Because some physicians do not screen annually by cytology, 12% of women did not receive a Pap test within 3 months of the enrollment exam and the HPV DNA test. Pap results were classified according to the most severe diagnosis as negative for intraepithelial lesion or malignancy (NILM), atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithial lesion (LSIL), atypical squamous cells, cannot exclude high-grade squamous intraepithial lesion (ASC-H), high-grade squamous intraepithial lesion (HSIL), or cancer. For study purposes abnormal cytology was considered ASCUS or greater.

Detection and genotyping of HPV DNA from cervical specimens of all women at baseline was performed at Johns Hopkins University in Baltimore, MD. DNA was extracted using the QIAamp DNA Blood Kit (Qiagen,Valencia, CA, USA) according to manufacturer's instructions with modification (11). An 8μl aliquot of extracted DNA was tested using the Roche HPV Linear Array PCR-based assay (Roche Diagnostics, Indianapolis, IN, USA). Detection of the presence of human DNA by beta-globin-specific polymerase chain reaction (PCR) is a component of the LA assay, and was used to determine sample adequacy. The HPV Linear Array is based on the PGMY09/11 PCR primer system that allows for high efficiency amplification of 37 distinct HPV genotypes (12, 13). For this analysis, HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 were classified as high-risk (carcinogenic) HPV types.

Statistical analysis

Descriptive analyses were conducted to characterize the pattern of HPV infection and cervical abnormalities among women in five-year age categories: 35–39, 40–44, 45–49, 50–54 and 55–60 years. The correlation between HPV-positivity and abnormal cervical cytology was examined by calculating the prevalence of HR-HPV detection among women with current abnormalities and the prevalence of abnormalities among women with detectable HR-HPV. To determine if the association between HPV and abnormalities changed with increasing age, a two-sided test for trend across ordered groups was performed with the significance level set at $p < 0.05$. Exact logistic regression was used to estimate unadjusted odds ratios and corresponding 95% confidence intervals for the association between potential risk factors for HPV positivity and cervical abnormalities. Regression analyses were conducted separately for women under the median age of 45 years and for

women 45 years and older. To examine correlates of abnormal cytology independent of HR-HPV infection, additional regression models were adjusted for the presence of HR-HPV. All analyses were carried out using SAS version 9.2 (SAS Institute, Cary, NC, USA).

RESULTS

Description of routinely screened perimenopausal women

Of the 949 women enrolled in this study, 101 women were excluded from this analysis because they did not have a Pap smear within 3 months of study enrollment, 64 women were excluded because of incomplete baseline questionnaire data, and 3 because their cervical samples for HPV DNA detection were beta-globin negative. In the remaining 781 women, the median age was 47 years (IQR: 41–52) and 64% (n=497) were currently married (Table 1). The majority of women were white (n=594, 74%) and had completed at least some education beyond high school (83%; n=651). All women reported having previous Pap smear screening, with over 90% (n=700) of women reporting a Pap smear in the 3 years prior to enrollment. Almost half of the women (46%; n=416) reported having received an abnormal Pap result prior to enrollment and 20% reported ever having a colposcopy (n=165) or treatment for an abnormal Pap smear (n=148).

Correlation between HPV positivity and abnormal cervical cytology

At baseline, the prevalence of any-HPV detection was 18% (n=142), the prevalence of HR-HPV detection was 9% (n=68), and the prevalence of cytologic abnormalities was 5% (n=40), which included 25 cases of ASCUS, 13 cases of LSIL and 2 cases of ASC-H. There was a significant decrease in the prevalence of any-HPV (p=0.003), HR-HPV (p<0.001), and abnormal cervical cytology (p<0.001) with age (Table 2). The decrease in prevalence from youngest to oldest was almost 5-fold for high-risk HPV, from 17% (23/137) to 4% (4/116). A similar decrease was seen for abnormal cytology, and no abnormalities were detected in the oldest group of women. Similar patterns were observed for combinations of concurrent Pap smear and HR-HPV DNA results by age (Table 3). Corresponding with the decreasing prevalence, the percentage of women who were negative on both tests increased, while those who were positive on both decreased with age.

There was a trend of decreased concordance between Pap and HR-HPV test results with age, but an increase in the concordance between Pap and any-HPV test results (Fig. 1). Specifically, among women with HR-HPV infection, there was a decrease in the proportion of cervical abnormalities with increasing age, from 30% (7/23) among women in the youngest age group to 0% (0/4) in the oldest. A similar decrease was seen in the proportion of abnormalities among women with any-HPV detected. Among women with abnormal cervical cytology, there was a decrease in the prevalence of HR-HPV with increasing age. In women aged 35–39 years, 50% (7/14) of women with cervical abnormalities had HR-HPV infection, whereas only 25% (1/4) of 50–54 year old women with cervical abnormalities had detectable HR-HPV. On the other hand, the prevalence of any-HPV among women with abnormal cytology was highest in the women 50–54 years old (75%; n=3).

Risk factors for current HPV and cervical abnormalities

To better understand the discordance between HR-HPV and cervical abnormalities with age, we made individual comparisons of the correlates of current HPV infection with the correlates of cervical abnormalities among women under and over 45 years of age (Table 4). The odds of HR-HPV detection were higher among unmarried women compared with married women in both age groups. In addition, the odds of HR-HPV detection were higher among women who reported a new sex partner in the last 6 months, regardless of age, compared with women without sexual partners.

Among younger women (under 45 years of age), there was a trend for higher odds of HR-HPV detection and cervical abnormalities among lower income women compared with women in the highest income level. In addition, self-reported history of colposcopy was associated with a higher odds of both HR-HPV (odds ratio [OR]: 2.6; (95% confidence interval [CI]: 1.3, 5.5)) and abnormalities (OR: 4.1 (1.6, 10.5)) at baseline. Women under 45 years of age who were single as compared to married (OR: 3.7 (1.6, 8.6)), current hormone users (OR: 2.1 (1.0, 4.2)), and women reporting recent new sexual partners (OR: 17.7 (5.6, 84.0)), had a higher odds of HR-HPV detection only, whereas women with previous abnormalities (OR: 3.4 (1.3, 9.9)) had a higher odds of a current cytological abnormalities but not current HR-HPV detection.

HR-HPV detection in women 45 years and older was associated with being unmarried (OR: 2.8 (1.0, 7.5)), having a lower income as compared to $120,000 (range OR: 2.5 (0.0, 49.5)) to 5.7 (1.1, 57.4)), being a current smoker as compared to never smoking (OR: 3.5 (1.1, 10.0)), having 5 or more lifetime sex partners (OR: 3.4 (1.2, 11.8)), having a recent new sex partner (OR: 8.5 (1.3, 41.9)), and having a history of an abnormal Pap smear (OR: 2.6 (1.1, 7.1)). Only women reporting a history of 3 or more births had higher odds of abnormal cervical cytology at baseline. No risk factors were associated with both HR-HPV detection and cervical abnormalities in older women.

In women age 45 and older, having a low-risk HPV infection was associated with a 6-fold higher odds of cytologic abnormality compared to women who were HPV-negative (Table 5). This association was not seen in younger women. The odds of cytologic abnormalities increased for current smokers under 45, after controlling for HR-HPV (OR: 4.4 (1.0, 16.8)). The 5-fold higher odds of cytologic abnormality associated with 3 or more live births in women over 45 remained consistent after controlling for HR-HPV. The association between a recent new sex partner and cervical abnormalities decreased by 68% in younger women but only decreased 42% in older women after adjusting for HR-HPV. Although the adjusted estimate was slightly lower than the unadjusted estimate, the odds of current abnormalities remained higher among women under 45 years of age who reported previous colposcopy.

DISCUSSION

Current cervical cancer screening guidelines group together all women age 30 and above (2, 3, 14). Our data raise important questions about the homogeneity of the interpretation of HPV and Pap test results in this age group. Although the relative proportion of low and high-grade abnormalities did not change with age, we saw a loss of concordance between HR-HPV detection and cytological abnormalities with increasing age. This discordance cannot be attributed to an increase in the proportion of ASCUS relative to higher-grade lesions in older women. ASCUS accounted for 57% of cervical abnormalities in women 35–39 years, 70% in women 40–44, 67% in women 45–49, and 50% in women age 50–54 years. Consistent with our findings, a decrease in the prevalence of HPV among all grades of abnormal cytology was also observed with increasing age in the Kaiser Permanente screening cohort of nearly one million women age 30–64 years (15). For example, among women with ASCUS and LSIL, 52% and 89% of 30–34 year olds compared with 28% and 75% of 60–64 year olds had HPV infection, respectively. An age-specific decline in the prevalence of cervical abnormalities among HPV-positive women was also reported in the Kaiser Permanente screening cohort. Several studies have shown that HPV testing among older women with low-grade abnormalities detected by cytology can help to distinguish between true infections that carry a risk for progression to cervical precancer and other morphological changes that are not associated with risk of cancer (16–18). This is in contrast to the findings from a large US randomized controlled trial, which concluded that there was limited value for HR-HPV triage of low-grade lesions (19). The young age of participants in

the ASCUS/LSIL Triage Study (mean, 27.9 years) limited the ability to make strong conclusions about HPV triage of LSIL in women over 30, although they did report a 2-fold lower HR-HPV DNA prevalence in the 18% of LSIL positive women who were over age 30 years.

Although the prevalence of HR-HPV decreased linearly with age among women with cytological abnormalities, the prevalence of any-HPV was U-shaped and highest among older women. This pattern would suggest that both LR-HPV and HR-HPV infection play a role in the detection of cervical abnormalities in older women. Indeed, there was a strong association between infection with only low-risk HPV types and cervical abnormalities in women over 45 years of age (OR: 6.4 (1.5, 24.8)) which was not observed in younger women (OR: 1.7 (0.2, 8.7)). This is consistent with two well-documented observations: the regression of the cervical transformation zone into the os in older women (20) and the higher prevalence of LR-HPV in vaginal compared with cervical epithelium (21).

An advantage of our study was the ability to compare the age-stratified correlates of HPV infection to the correlates of abnormal cytology. The correlates of HPV were generally similar in younger and older women. A notable exception was the association seen only in older women between HPV detection and a higher number of self-reported lifetime sex partners, suggesting that HPV in older women is more likely to represent long-term persistent infection (22, 23). The correlates of HPV were similar to the correlates of cervical abnormalities among younger women aged 30–44 years. However, in older women, the variables we expected to be correlated with both HPV and abnormalities, given the strong causal link between HPV and cervical abnormalities, were only seen for HPV infection. Although these findings are consistent with the observed decreased correlation between HR-HPV infection and cervical abnormalities in older women, the explanation for these differences is not clear.

The overall prevalence of cervical abnormalities in our population was low and no abnormalities were detected among the 116 women age 55–60 years. In addition, most abnormalities were low-grade (ASCUS and LSIL), which is likely due to the low-risk characteristics and high level of prior screening in this population. The relatively small sample size limited our ability to evaluate the significance of the loss of HPV-Pap correlation on the screening performance of either test at older ages. While the low number of abnormal cytology results limits our ability to make firm conclusions, our data suggest that the typical determinants for testing positive for two common markers of neoplasia used in screening (cytology and HPV DNA) may be different in 35–45 vs. 45–60 year old women, and suggest the need for a more detailed review of the specificity of these markers in perimenopausal women. The age-stratified analyses suggest that the abnormalities detected in older women are potentially related to LR-HPV infection or age-related morphological changes, as well as HR-HPV infection. However, we do not have pathologic confirmation to gain a clearer understanding of the differences in the sensitivity and specificity of HPV testing and cervical cytology in women over age 45 years. In the Kaiser Permanente screening cohort, the risk of CIN3+ among HPV−/Pap+ tended to be higher in older compared with younger women, while the risk of CIN3+ decreased with increasing age among HPV+/Pap− women (online supplement (10)).

With the consensus guidelines from the ASCCP recommending Pap smear screening with adjunctive HPV testing in women over 30 years of age, and increasing numbers of women asking for the test, HPV testing in women over 30 is on the rise. Still, controversy remains over the most appropriate use of HPV testing and cytology in older women. Recently, the U.S. Preventive Services Task Force did not include guidelines on the use of HPV testing in primary screening of perimenopausal and older women, citing the lack of evidence on which

to base recommendations (14). We found that detection of HR-HPV and cytological abnormalities is not uniform among all women over 30 years of age, and neither is the correlation between these measures of risk of cervical precancer. These data suggest that ongoing surveillance of the performance of HPV and cytology in cervical cancer screening programs should consider a third age stratification at 45 years and above. Castle, *et al.*, previously suggested a similar age-stratified approach for the use of HPV testing in the triage of women 45 to 50 years and older with low-grade abnormalities (15). The relevance of HPV and Pap test performance in older women will increase as cohorts of more highly exposed women age. Therefore, additional follow-up is needed in this cohort to observe the natural history of HPV infection and clarify the clinical relevance of positive HPV and Pap smear testing outcomes in older women.
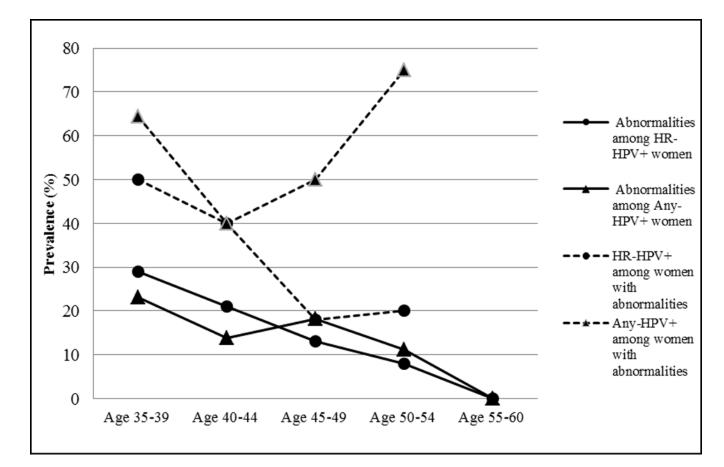
Acknowledgments

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Figure 1.
The correlation between abnormal cervical cytology and HR-HPV DNA detection stratified by age.
Abbreviations: HR-HPV+=positive for high-risk human papillomavirus types; Any-HPV +=positive for any human papillomavirus types

Table 1

Characteristics of the mid-adult screening population (N=781)

	Total cohort N(%)
Age in years	
35–39	137 (18)
40–44	172 (22)
45–49	195 (25)
50–54	161 (21)
55–60	116 (15)
Marital status[1]	
Married	497 (64)
Divorced/Separated/Widowed	143 (18)
Single	140 (18)
Race	
White/Caucasian	579 (74)
Black/African-American	146 (19)
Other	56 (7)
Education completed	
High School	130 (17)
Post high school	182 (23)
College	231 (30)
Post graduate	238 (30)
Yearly Income (US dollars)	
<40,000	54 (7)
40–80,000	186 (24)
80–120,000	175 (22)
>120,000	234 (30)
unknown	132 (17)
BMI	
<25	301 (39)
25–29.9	236 (30)
>30	243 (31)
Smoking history	
Never	538 (69)
Former	159 (20)
Current smoker	84 (11)
Exogenous Hormone Use[2]	
Never/Former	582 (75)
Current	199 (25)
Menopausal status	
Premenopausal	329 (43)

	Total cohort N(%)
Perimenopausal	231 (30)
Postmenopausal	203 (27)
Live Births	
0	220 (28)
1	140 (18)
2	280 (36)
3 or more	139 (18)
Lifetime number of sexual partners	
0–1	105 (14)
2	56 (7)
3	79 (10)
4	64 (8)
5	95 (12)
6–10	212 (27)
11–20	109 (14)
>20	58 (7)
Recent sexual partners[3]	
No recent sex	162 (21)
Sex, no new partner	591 (76)
Sex with new partner(s)	23 (3)
Ever diagnosed with STI(s)[4]	
No	507 (65)
Yes	270 (35)
Ever previous Pap screening	
Yes	781 (100)
Ever previous Abnormal Pap	
No	416 (54)
Yes	356 (46)
Ever had colposcopy	
No	616 (79)
Yes	165 (21)
Ever treated for abnormal Pap[5]	
No	633 (81)
Yes	148 (19)

[1]Widowed (n=13), separated (n=26), divorced (n=104), 1 missing marital status

[2]Includes both hormonal contraceptives and hormone replacement therapy

[3]Recent refers to the 6 months prior to study baseline

[4]Includes chlamydia, gonorrhea, herpes, trichomonas, syphilis, chancroid, and genital warts

[5]Treatment defined as laser, cryotherapy, LEEP, or conization

Missing data: marital status-1, bmi-1, menopausal status-18, live births-2, lifetime number of sexual partners-3, recent sex-5, ever diagnosed with STI-4, previous abnormal pap- 9

Abbreviations: N=number, %=percent, BMI=body mass index, STI=sexually transmitted infection

Table 2

The prevalence of HPV and cervical abnormalities across age strata among women over 35 years old.

	Any-HPV DNA		HR-HPV DNA[1]		Only LR-HPV DNA		Cervical cytology	
	Negative N (%)	Positive N (%)	Negative N (%)	Positive N (%)	Negative N (%)	Positive N (%)	Normal N (%)	Abnormal[2] N (%)
Age 35–39 (n=137)	98 (72)	39 (28)	114 (83)	23 (17)	121 (88)	16 (12)	123 (90)	14 (10)
Age 40–44 (n=172)	143 (83)	29 (17)	153 (89)	19 (11)	162 (94)	10 (6)	162 (94)	10 (6)
Age 45–49 (n=195)	162 (83)	33 (17)	182 (93)	13 (7)	175 (90)	20 (10)	183 (94)	12 (6)
Age 50–54 (n=161)	134 (83)	27 (17)	152 (94)	9 (6)	143 (89)	18 (11)	157 (98)	4 (2)
Age 55–60 (n=116)	102 (82)	14 (12)	112 (97)	4 (3)	106 (91)	10 (9)	116 (100)	0 (0)
Trend p-value	0.003		<0.001		0.924		<0.001	

[1] HR-HPV with or without LR-HPV infection

[2] Abnormal is defined as ASCUS (ASCUS=25, LSIL=13, ASC-H=2, HSIL=0)

Abbreviations: HPV=high-risk human papillomavirus, HR=high-risk, LR=low-risk,N=number, %=percentage, ASCUS=atypical squamous cells, undetermined significance, LSIL=low-grade intraepithelial lesion, ASC-H=atypical squamous cells, can't exclude high-grade squamous intraepithelial lesion, HSIL= high-grade squamous intraepithelial lesion

Table 3

Correlation between HR-HPV and cytology results stratified by age[1]

	HPV– Pap- N (%)	HPV+ Pap- N (%)	HPV– Pap+ N (%)	HPV+ Pap+ N (%)
35–39 (n=137)	107 (78)	16 (12)	7 (5)	7 (5)
40–44 (n=172)	147 (85)	15 (9)	6 (3)	4 (2)
45–49 (n=195)	173 (89)	10 (5)	9 (5)	3 (2)
50–54 (n=161)	149 (93)	8 (5)	3 (2)	1 (1)
55–60 (n=116)	112 (97)	4 (3)	0 (0)	0 (0)
Trend p-value	<0.001	0.003	0.02	0.002

[1]Categories are mutually exclusive combinations of HR-HPV DNA status and Pap Smear results: HR-HPV negative and normal Pap, HR-HPV positive and normal Pap, HR-HPV negative and ASCUS, HR-HPV positive and ASCUS

Abbreviations: HPV=high-risk human papillomavirus, HR=high-risk, N=number, %=percentage, ASCUS=atypical squamous cells, undetermined significance

Table 4

Correlates of HR-HPV infection and cervical abnormalities stratified by age.

	Women <45 years				Women 45 years			
	HR-HPV [n(%)]	uOR [95% CI]	Abnormal [n(%)]	uOR [95% CI]	HR-HPV [n(%)]	uOR [95% CI]	Abnormal [n(%)]	uOR [95% CI]
Marital status								
Married	15 (8)	REF	14 (8)	REF	12 (4)	REF	10 (3)	REF
Divorced/Separated/Widowed	10 (19)	2.6 (1.0, 6.6)	5 (9)	1.2 (0.3, 3.9)	9 (10)	2.8 (1.0, 7.5)	3 (3)	1.1 (0.2, 4.2)
Single	17 (25)	3.7 (1.6, 8.6)	5 (7)	1.0 (0.3, 3.0)	5 (7)	1.9 (0.5, 6.0)	3 (4)	1.3 (0.2, 5.3)
Race								
White/Caucasian	27 (13)	REF	16 (8)	REF	19 (5)	REF	14 (4)	REF
Black/African-American	10 (14)	1.1 (0.5, 2.6)	6 (9)	1.1 (0.3, 3.2)	5 (7)	1.2 (0.4, 3.8)	1 (1)	0.3 (0.0, 2.3)
Other	5 (17)	1.3 (0.4, 4.0)	2 (7)	0.9 (0.1, 4.0)	2 (8)	1.5 (0.2, 7.0)	1 (4)	1.0 (0.0, 7.2)
Education completed								
High School	6 (11)	REF	4 (7)	REF	3 (4)	REF	3 (4)	REF
Post high school	15 (22)	2.3 (0.8, 8.0)	10 (15)	2.2 (0.6, 10.3)	10 (9)	2.3 (0.6, 13.3)	3 (3)	0.6 (0.1, 4.9)
College	13 (13)	1.3 (0.4, 4.3)	3 (3)	0.4 (0.1, 2.5)	6 (5)	1.1 (0.2, 7.2)	3 (2)	0.6 (0.1, 4.2)
Post graduate	8 (9)	0.9 (0.2, 3.2)	7 (8)	1.2 (0.3, 5.6)	7 (5)	1.1 (0.3, 7.1)	7 (5)	1.1 (0.3, 7.0)
Yearly Income								
>120,000	6 (7)	REF	3 (4)	REF	2 (1)	REF	6 (4)	REF
80–120,000	10 (13)	1.9 (0.6, 6.7)	6 (8)	2.2 (0.5, 14.2)	7 (7)	5.7 (1.1, 57.4)	2 (2)	0.5 (0.1, 2.9)
40–80,000	16 (18)	2.8 (1.0, 9.2)	12 (14)	4.1 (1.1, 23.7)	7 (7)	5.7 (1.1, 57.4)	3 (3)	0.8 (0.1, 3.7)
<40,000	2 (8)	1.2 (0.1, 7.3)	1 (4)	1.2 (0.0, 15.5)	1 (3)	2.5 (0.0, 49.5)	3 (10)	2.6 (0.4, 13.1)
Unknown	8 (19)	2.9 (0.8, 11.0)	2 (5)	1.3 (0.1, 11.8)	9 (10)	8.3 (1.7, 80.9)	2 (2)	0.6 (0.1, 3.2)
Smoking history								
Never	34 (15)	REF	14 (6)	REF	13 (4)	REF	10 (3)	REF
Former	6 (12)	0.7 (0.2, 1.9)	5 (10)	1.6 (0.4, 5.0)	6 (6)	1.4 (0.4, 4.0)	5 (5)	1.5 (0.4, 4.9)
Current smoker	2 (7)	0.4 (0.0, 1.7)	5 (16)	2.9 (0.8, 9.4)	7 (13)	3.5 (1.1, 10.0)	1 (2)	0.6 (0.0, 4.2)
Live Births								
0	10 (16)	REF	5 (8)	REF	3 (4)	REF	1 (1)	REF
1	8 (18)	0.8 (0.2, 2.3)	3 (9)	0.6 (0.1, 2.7)	6 (8)	1.0 (0.2, 3.7)	0 (0)	1.4 (0.1, 19.4)
2	7 (11)	0.6 (0.3, 1.5)	6 (10)	0.6 (0.2, 1.9)	8 (6)	1.0 (0.3, 3.3)	5 (4)	2.0 (0.3, 21.2)

	Women <45 years				Women 45 years			
	HR-HPV [n(%)]	uOR [95% CI]	Abnormal [n(%)]	uOR [95% CI]	HR-HPV [n(%)]	uOR [95% CI]	Abnormal [n(%)]	uOR [95% CI]
3 or more	17 (12)	0.9 (0.3, 2.6)	10 (7)	1.0 (0.2, 3.5)	9 (5)	0.8 (0.2, 3.4)	10 (5)	5.5 (1.0, 55.3)
Exogenous Hormone Use								
Never/ Former	21 (11)	REF	13 (7)	REF	21 (6)	REF	15 (4)	REF
Current	21 (19)	2.1 (1.0, 4.2)	11 (10)	1.6 (0.6, 4.1)	5 (6)	1.0 (0.3, 2.8)	1 (1)	0.3 (0.0, 1.8)
Lifetime sex partners								
< 5	11 (11)	REF	5 (5)	REF	5 (3)	REF	10 (5)	REF
5	31 (15)	1.4 (0.7, 3.3)	19 (9)	1.9 (0.7, 6.7)	21 (8)	3.4 (1.2, 11.8)	6 (2)	0.5 (0.1, 1.4)
Recent sex partners								
Sex, no new partner(s)	28 (11)	REF	17 (7)	REF	16 (5)	REF	12 (4)	REF
No recent sex	4 (10)	0.9 (0.2, 2.9)	3 (8)	1.2 (0.2, 4.3)	7 (6)	1.2 (0.4, 3.2)	2 (2)	0.5 (0.1, 2.1)
Sex with new partner(s)	9 (69)	17.7 (5.6, 84.0)	3 (23)	4.1 (0.7, 18.2)	3 (30)	8.5 (1.3, 41.9)	2 (20)	6.7 (0.6, 39.2)
Ever previous abnormality								
No	18 (10)	REF	7 (4)	REF	8 (3)	REF	8 (3)	REF
Yes	24 (18)	1.8 (0.9, 3.8)	17 (13)	3.4 (1.3, 9.9)	18 (8)	2.6 (1.1, 7.1)	8 (4)	1.1 (0.4, 3.5)
Time since last abnormal pap [1]								
No abnormal pap	18 (10)	REF	7 (4)	REF	8 (3)	REF	8 (3)	REF
1–5 years	6 (14)	1.4 (0.4, 4.0)	4 (9)	2.4 (0.5, 10.1)	6 (9)	2.8 (0.8, 9.7)	2 (3)	0.9 (0.1, 4.6)
6–10 years	4 (15)	1.6 (0.4, 5.4)	5 (19)	5.6 (1.3, 22.6)	5 (14)	4.9 (1.8, 18.1)	0 (0)	0.6 (0.0, 4.1)
>10 years	9 (16)	1.6 (0.6, 4.0)	4 (7)	1.8 (0.4, 7.2)	4 (4)	1.2 (0.3, 4.8)	0 (0)	0.2 (0.0, 1.4)
Ever previous colposcopy								
No	24 (10)	REF	11 (5)	REF	17 (4)	REF	11 (3)	REF
Yes	18 (23)	2.6 (1.3, 5.5)	13 (17)	4.1 (1.6, 10.5)	9 (10)	2.5 (0.9, 6.1)	5 (6)	2.0 (0.5, 6.6)

[1] N=744; 21 excluded because abnormal Pap within 1 year of enrollment and so could not be conclusively separated from baseline result, 16 excluded because missing abnormal Pap date

Abbreviations: N=number, %=percent, HR-HPV=high-risk human papillomavirus, uOR=unadjusted odds ratio, CI=confidence interval, REF=referent group

Table 5

Correlates of cervical abnormalities independent of HR-HPV infection, stratified by age.

	Women <45 years			Women ≥45 years		
	Abnormal [n(%)]	uOR [95% CI]	aOR [95% CI] [1]	Abnormal [n(%)]	uOR [95% CI]	aOR [95% CI] [1]
HPV risk groups						
None	11 (5)	REF		7 (2)	REF	
Low-risk Only	2 (8)	1.7 (0.2, 8.7)		5 (10)	6.4 (1.5, 24.8)	
Low-risk + High-risk	5 (33)	10.2 (2.3, 40.6)		2 (17)	11.0 (1.0, 68.8)	
High-risk Only	6 (22)	5.9 (1.6, 19.6)		2 (14)	9.2 (0.8, 55.8)	
Marital status						
Married	14 (8)	REF	REF	10 (3)	REF	REF
Divorced/Separated/Widowed	5 (9)	1.2 (0.3, 3.9)	0.9 (0.2, 3.0)	3 (3)	1.1 (0.2, 4.2)	0.8 (0.1, 3.5)
Single	5 (7)	1.0 (0.3, 3.0)	0.6 (0.1, 1.9)	3 (4)	1.3 (0.2, 5.3)	1.2 (0.2, 4.8)
Race						
White/Caucasian	16 (8)	REF	REF	14 (4)	REF	REF
Black/African-American	6 (9)	1.1 (0.3, 3.2)	1.1 (0.3, 3.2)	1 (1)	0.3 (0.0, 2.3)	0.3 (0.0, 2.2)
Other	2 (7)	0.9 (0.1, 4.0)	0.8 (0.1, 2.8)	1 (4)	1.0 (0.0, 7.2)	0.9 (0.0, 6.9)
Education completed						
High School	4 (7)	REF	REF	3 (4)	REF	REF
Post high school	10 (15)	2.2 (0.6, 10.3)	1.7 (0.4, 8.4)	3 (3)	0.6 (0.1, 4.9)	0.5 (0.1, 4.1)
College	3 (3)	0.4 (0.1, 2.5)	0.4 (0.1, 2.3)	3 (2)	0.6 (0.1, 4.2)	0.5 (0.1, 4.2)
Post graduate	7 (8)	1.2 (0.3, 5.6)	1.2 (0.3, 6.2)	7 (5)	1.1 (0.3, 7.0)	1.1 (0.1, 4.1)
Yearly Income						
>120,000	3 (4)	REF	REF	6 (4)	REF	REF
80–120,000	6 (8)	2.2 (0.5, 14.2)	1.9 (0.4, 23.5)	2 (2)	0.5 (0.1, 2.9)	0.4 (0.0, 2.2)
40–80,000	12 (14)	4.1 (1.1, 23.7)	3.2 (0.8, 19.1)	3 (3)	0.8 (0.1, 3.7)	0.6 (0.1, 2.9)
<40,000	1 (4)	1.2 (0.0, 15.5)	1.1 (0.0, 15.6)	3 (10)	2.6 (0.4, 13.1)	2.4 (0.4, 14.5)
unknown	2 (5)	1.3 (0.1, 11.8)	0.9 (0.1, 8.8)	2 (2)	0.6 (0.1, 3.2)	0.4 (0.0, 2.2)
Smoking history						
Never	14 (6)	REF	REF	10 (3)	REF	REF
Former	5 (10)	1.6 (0.4, 5.0)	1.9 (0.5, 6.6)	5 (5)	1.5 (0.4, 4.9)	1.4 (0.4, 4.7)

	Women <45 years			Women ≥45 years		
	Abnormal [n(%)]	uOR [95% CI]	aOR [95% CI] [1]	Abnormal [n(%)]	uOR [95% CI]	aOR [95% CI] [1]
Current smoker	5 (16)	2.9 (0.8, 9.4)	4.4 (1.0, 16.8)	1 (2)	0.6 (0.0, 4.2)	0.4 (0.0, 3.2)
Live Births						
0	5 (8)	REF	REF	1 (1)	REF	REF
1	3 (9)	0.6 (0.1, 2.7)	0.7 (0.1, 3.1)	0 (0)	1.4 (0.1, 19.4)	1.4 (0.1, 19.8)
2	6 (10)	0.6 (0.2, 1.9)	0.7 (0.2, 2.2)	5 (4)	2.0 (0.3, 21.2)	2.0 (0.3, 21.6)
3 or more	10 (7)	1.0 (0.2, 3.5)	1.0 (0.2, 3.8)	10 (5)	5.5 (1.0, 55.3)	5.9 (1.1, 60.8)
Exogenous Hormone Use						
Never/ Former	13 (7)	REF	REF	15 (4)	REF	REF
Current	11 (10)	1.6 (0.6, 4.1)	1.3 (0.5, 3.4)	1 (1)	0.3 (0.0, 1.8)	0.3 (0.0, 1.8)
Lifetime sex partners						
< 5	5 (5)	REF	REF	10 (5)	REF	REF
5	19 (9)	1.9 (0.7, 6.7)	1.7 (0.6, 6.3)	6 (2)	0.5 (0.1, 1.4)	0.3 (0.1, 1.1)
Recent sex partners						
Sex, no new partner(s)	17 (7)	REF	REF	12 (4)	REF	REF
No recent sex	3 (8)	1.2 (0.2, 4.3)	1.2 (0.2, 4.8)	2 (2)	0.5 (0.1, 2.1)	0.4 (0.1, 2.0)
Sex with new partner(s)	3 (23)	4.1 (0.7, 18.2)	1.3 (0.2, 7.0)	2 (20)	6.7 (0.6, 39.2)	3.9 (0.3, 26.3)
Ever previous abnormality						
No	7 (4)	REF	REF	8 (3)	REF	REF
Yes	17 (13)	3.4 (1.3, 9.9)	2.9 (1.1, 8.9)	8 (4)	1.1 (0.4, 3.5)	0.9 (0.3, 2.9)
Time since last abnormal pap [1]						
No abnormal pap	7 (4)	REF	REF	8 (3)	REF	REF
2–5 years	4 (9)	2.4 (0.5, 10.1)	2.3 (0.4, 9.8)	2 (3)	0.9 (0.1, 4.6)	0.8 (0.1, 4.4)
6–10 years	5 (19)	5.6 (1.3, 22.6)	5.4 (1.2, 22.9)	0 (0)	0.6 (0.0, 4.1)	0.6 (0.0, 3.8)
>10 years	4 (7)	1.8 (0.4, 7.2)	1.6 (0.3, 6.6)	0 (0)	0.2 (0.0, 1.4)	0.2 (0.0, 1.4)
Ever previous colposcopy						
No	11 (5)	REF	REF	11 (3)	REF	REF
Yes	13 (17)	4.1 (1.6, 10.5)	3.2 (1.2, 8.6)	5 (6)	2.0 (0.5, 6.6)	1.7 (0.4, 5.6)

[1] Adjusted for the presence of HR-HPV (N=744)

Abbreviations: N=number, %=percent, HR-HPV=high-risk human papillomavirus, uOR=unadjusted odds ratio, aOR=adjusted odds ratio, CI=confidence interval, REF=referent group