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Risk Factors for Persistent Cervical Intraepithelial Neoplasia Grades 1 and 2 Managed by Watchful Waiting

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Abstract

Objective—This study examines risk factors for persistent cervical intraepithelial neoplasia (CIN) and whether human papillomavirus (HPV) testing predicts persistent lesions.

Materials and Methods—Women with histologically diagnosed CIN 1 or CIN 2 (n = 206) were followed every 3 months without treatment. HPV genotyping, plasma levels of ascorbic acid, and red blood cell folate were obtained. Cervical biopsy at 12 months determined the presence of CIN. Relative risk (RR) was estimated by log-linked binomial regression models.

Results—At 12 months, 70% of CIN 1 versus 54% of CIN 2 lesions spontaneously regressed ($p < 0.001$). Levels of folate or ascorbic acid were not associated with persistent CIN at 12 months. Compared to HPV negative women, those with multiple HPV types (RRs ranged from 1.68 to 2.17 at each follow-up visit) or high-risk types (RRs range = 1.74 to 2.09) were at increased risk for persistent CIN; women with HPV 16/18 had the highest risk (RRs range = 1.91 to 2.21). Persistent infection with a high-risk type was also associated with persistent CIN (RRs range = 1.50 – 2.35). Typing for high-risk HPVs at 6 months only had a sensitivity of 46% in predicting persistence of any lesions at 12 months.

Conclusion—Spontaneous regression of CIN 1 and CIN 2 occurs frequently within 12 months. HPV infection is the major risk factor for persistent CIN. However, HPV testing cannot reliably predict persistence of any lesion.

Keywords

cervical intraepithelial neoplasia; human papillomavirus

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INTRODUCTION

Some cervical intraepithelial neoplasia (CIN) lesions progress to cervical cancer. Most of them, particularly CIN 1 and 2 lesions, regress spontaneously without treatment [1–3]. Current consensus guidelines recommend follow up with cytology for up to 2 years for some women with CIN [4]. Conservative management avoids complications and excessive costs from overtreatment, but some women may not comply with repeat cervical cytology. Early identification of lesions likely to persist or progress may indicate when immediate treatment is preferred.

We analyzed data from a prospective study, in which women with histologically confirmed CIN 1 or CIN 2 were followed at 3-month intervals for one year without treatment, to identify risk factors associated with persistent CIN at 12 months. Human papillomavirus (HPV) infection, histologic findings, reproductive factors, sexual behavior, plasma ascorbic acid, and red blood cell (RBC) folate levels were assessed.

MATERIALS AND METHODS

Study Population and Clinical Procedures

Study protocol was approved by the institutional review boards of four participating institutions. Women who had a cervical biopsy at the colposcopy clinic in one of the four participating hospitals in New York City between August 1995 and May 2003 were potentially eligible for this study. When women returned to the clinic for their biopsy results, they were screened for the following eligibility criteria: (1) having a histological diagnosis of CIN 1 or CIN 2 determined by hospital staff pathologists; (2) the lesion was a “new” diagnosis defined as no prior CIN diagnosis or treatment within the last 12 months; (3) satisfactory colposcopy; (4) age ≥ 18 years old; (5) not pregnant at the time of recruitment; and (6) recruitment within 4 months of CIN diagnosis. Those who were eligible and agreed to participate signed an informed consent and completed the baseline visit procedures. Thereafter, they were followed conservatively without treatment at 3, 6, 9, and 12 months. Endpoint biopsy was performed at the 12-month visit. This prospective study was implemented when consensus guidelines for the management of women with CIN were not available. The 12-month follow-up time and inclusion of women with CIN 2 in the study were determined based on our previous data that showed follow-up of these women was safe and no subjects developed cervical cancer in 12 months [5].

At each visit, a questionnaire was administered to obtain information on the subject’s demography, sexual and lifestyle behaviors, as well as reproductive and medical histories. The status of CIN was monitored by Pap smear, which was taken by the scrape/swab technique with a wooden spatula and cotton tip applicator, and by colposcopic examination without digital imaging. Samples of cervicovaginal lavage for HPV testing and peripheral blood were collected [6].

Endpoint biopsy of any visible cervical abnormality was done at 12 months; if no lesion was seen, biopsy was performed at the original site of entry biopsy. For women who completed the study, pathology slides of their initial and endpoint biopsies were reviewed by the study pathologist (A.K.), who was blinded to the paired biopsies. If the histopathological review did not agree with the official diagnosis made by the hospital staff pathologists with respect to the severity of CIN, CIN grade determined by the study pathologist was used. However, if the review and official diagnosis differed in terms of presence or absence of a CIN lesion, then a second study pathologist (M.A.) served as the referee. Pap smear taken at the time of

initial biopsy or at 12 months was reviewed only if the cervical biopsy taken at the same visit was negative for CIN as determined by the review, but Pap smear was abnormal.

A total of 379 women were recruited, and 294 (77.6%) completed the 12-month visit and had an endpoint biopsy. Women with and without an endpoint biopsy were similar in terms of race/ethnicity, initial CIN grade, and HPV positivity at baseline. Of these 294 women, 79 (26.7%) were deemed ineligible for data analysis because their entry biopsies were reclassified as negative by the study pathologists. This percentage of over-diagnosis by hospital staff pathologists was in fact lower than what had been reported in other studies, in which diagnoses were compared between community pathologists and expert reviewers.[7, 8] Another 9 (4.2%) were excluded due to insufficient endpoint biopsy materials for outcome evaluation. The remaining 206 (70.1%) women who had histologically confirmed CIN 1 or CIN 2 at entry were included in data analysis.

Laboratory Procedures

Plasma prepared from heparinized blood samples collected at each study visit was assayed for reduced ascorbic acid by high pressure liquid chromatography (HPLC) method [inter-assay coefficient of variation (CV) < 5%] [9]. RBC folate levels were measured using a Bayer Corp. Immuno 1 autoanalyzer (Tarrytown, NY); inter-assay CVs at mean concentration (ng/mL) of 131 and 457 were 13% and 4%, respectively. DNA from cervicovaginal cells was tested for HPV DNA by both polymerase chain reaction (PCR) and Southern blot hybridization techniques in the first 4 years of the study and by PCR only beginning in 2000 [10]. PCR was performed using consensus primers (MY09 & MY11) to a highly conserved region in the L1 open reading frame [11]. Serum samples at each visit were tested for IgG antibodies to the synthetically produced virus-like particles (VLP) for HPV16 by a modified polymer ELISA [12, 13].

Statistical Analysis

The outcome of CIN was dichotomized as (1) complete regression: when both endpoint biopsy and Pap smear at 12 months were negative for CIN, versus (2) persistence: presence of CIN at 12 months determined by histological and/or cytological review. Pap smear at 12 months was used to determine persistence only when the endpoint cervical biopsy was negative for CIN by expert review, but Pap smear was confirmed by the study pathologist to be abnormal. Since persistent CIN is not a rare event, odds ratio is no longer an appropriate estimate of relative risk (RR) [14]. We obtained estimates of RR and their 95% likelihood ratio confidence intervals for the associations of persistent CIN with various risk factors using log-linked binomial regression models for both univariable and multivariable analyses [15].

Host factors included various baseline questionnaire variables (e.g., age, race/ethnicity, smoking, and sexual behavior, etc.), plasma levels of reduced ascorbic acid, and RBC folate. Levels of ascorbic acid and folate were measured at each study visit; mean levels were calculated over all visits and categorized into tertiles. Viral factors included IgG antibodies to VLP16, HPV positivity, HPV types, and number of HPV types, which were assessed at each visit. For VLP16 antibodies, the number of seropositive visits was analyzed. High-risk HPV types included HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68; all other HPV types, including the uncharacterized types, were classified as low-risk. In some analyses, HPV types were classified as (1) 16 or 18, (2) high-risk types other than HPV 16 or 18, and (3) all other types [16, 17]. If a subject was infected with multiple types, assignment to the higher risk group took precedence. To assess the aggregate effect of HPV over 12 months, the proportion of HPV positive visits was calculated as the number of HPV

positive visits divided by the number of visits completed by the subject who had at least 3 visits with known HPV results.

To evaluate the validity of HPV testing and in combination with cytology and/or colposcopy in dichotomizing women into two groups – spontaneous regression versus persistent CIN – the area under the ROC curve (AUC) was obtained using various classification variables defined by HPV results alone or HPV with cytology/colposcopy results [18]. ROC analyses were performed using MedCalc for Windows, version 11.4.1.0 (MedCalc Software, Mariakerke, Belgium). The statistical software package SAS 9.1 (SAS Institute Inc, Cary, NC) was used for all other analyses, and 2-tailed p values are presented.

RESULTS

The mean age of 206 study subjects was 29.8 years (SD = 9.2). The ethnic distribution was 63.6% Hispanic, 29.6% African Americans, and 6.8% non-Hispanic whites. At baseline, 143 (69.4%) women had confirmed CIN 1 and 63 (30.6%) had CIN 2. At 12 months, 72 women (35.0%) had a persistent lesion, including 5 (2.4%) who had CIN 3 on their endpoint biopsy, and there were no cases of invasive carcinoma (Table 1). Initial CIN status was associated with the severity of CIN at 12 months. Table 1 shows that 23.8% of women who had CIN 2 at baseline versus 4.9% of women who had CIN 1 initially had either CIN 2 or CIN 3 at 12 months (p for trend < 0.001). The RR for persistent CIN at 12 months was 1.53 (95% CI = 1.05 – 2.20) when women with CIN 2 at baseline were compared to those with CIN 1 (p = 0.023).

Table 2 shows the univarable results of host and viral factors associated with persistent CIN at 12 months. In addition to the initial CIN grade, presence of abnormal mitosis in squamous epithelial cells in cervical biopsy was a risk factor for persistent CIN. Less than a high school education and early menarche before the age of 13 were associated with persistent CIN, whereas other host factors, including age, race/ethnicity, current smoking, use of oral contraceptive pills, previous diagnosis of CIN, sexual behavior, RBC folate, or plasma levels of ascorbic acid, were not. HPV at baseline was not predictive of subsequent CIN outcome. However, subjects who had HPV detected in multiple visits, particularly in ≥75% of the visits, were 2.3 times more likely to have persistent CIN than those who were HPV negative throughout the study period (p for trend = 0.003). Seropositivity of VLP16 IgG antibodies was not associated with persistent CIN, even when the analyses were limited to women who had HPV16 or its related types (HPV 31,33,35,52,58) at baseline (data not shown).

In multivariable analyses (Table 3), after adjusting for HPV positivity throughout the study period, less than a high school education remained to be an independent risk factor of persistent CIN. Initial CIN grade at study entry became borderline significant (p = 0.07). None of the other host and histological factors were significant after adjusting for these three factors.

We further examined HPV infection and CIN outcome, adjusting for education and initial CIN grade. Table 4 shows that HPV positivity at each follow-up visit, and particularly, women infected with a high-risk HPV type or with multiple HPV types had an increased risk for persistent CIN. Furthermore, HPV 16/18 was associated with the highest risk for persistent CIN. For example, at the 6-month visit, compared to HPV negative women, the RRs for persistent CIN increased from 1.37 for women with a low-risk HPV (p = 0.307), to 1.83 for those with a non-16/18 high-risk type (p = 0.011), and further to 2.02 (p = 0.003) for those with HPV 16/18 (p for trend = 0.001); similar significant trend was also observed for other follow-up visits. Nevertheless, the difference in risk for persistent CIN was not

statistically significant when women with HPV 16/18 were compared with those with a non-16/18 high-risk type. When HPV types at the baseline and follow-up visits were considered together, we found that persistent infection with the same high-risk type was associated with a 2-fold increased risk for persistent CIN. Interestingly, women who acquired a new HPV type that was not detected at baseline [i.e., subjects who were (−,+) or (+,+) with a different type at baseline and follow-up visits] were also at risk for having CIN at 12 months (RRs ranged from 1.62 to 2.34 at each follow-up visit).

The current management strategy for women with CIN 1 or young women with CIN 2 is to follow conservatively every 6 to 12 months. We therefore examined whether HPV testing in combination with cytology and/or colposcopy results at the 6-month visit could predict the presence of CIN at 12 months and hence identify women who would benefit from early treatment of CIN. We examined the sensitivity and specificity of typing for high-risk HPV types, since they were significantly associated with persistent CIN (both 16/18 and non-16/18 high-risk types) and commercial kits are available for clinical testing. Table 5 shows that typing for high-risk HPVs had a sensitivity of 45.9% (95% CI = 33.4–58.4). HPV testing alone or in combination with cytology and/or colposcopy results correctly classified the outcome status of CIN at 12 months about 60% of the time. Typing for high-risk HPVs at other follow-up visits yielded similar predictive values (data not shown). Using HPV 16/18 typing at 6 months to predict CIN outcome missed many persistent lesions and yielded a low sensitivity of 21.3% (95% CI = 11.0–31.6).

DISCUSSION

In this study, 70% of CIN 1 and 54% of CIN 2 lesions spontaneously regressed within a year of initial biopsy. Our data were consistent with those from other follow-up studies on women with histologically diagnosed CIN in that the majority of mild to moderate lesions spontaneously regress and risk for progression to CIN 3 or cervical cancer is low [1–3].

We did not find high levels of plasma ascorbic acid and RBC folate to affect prognosis of CIN, although they have been suggested to be associated with reduced prevalence of CIN in previous cross-sectional studies [19, 20] and with decreased risk for type-specific persistent HPV infection [21]. A less than a high-school education was significantly associated with persistent CIN despite adjustment for various host and viral factors. Our data did not suggest any biological factors that might potentially mediate the association between educational level and persistent CIN.

Similar to previous studies, we found that the major risk factors for persistent CIN at 12 months were related to HPV infection [5, 22, 23]. Nevertheless, there are two noteworthy observations from our study. First, not only women who had persistent infection with a high-risk type from baseline were at risk for persistent CIN, but also those who acquired new previously undetected types during follow-up. Therefore, the presence of CIN during follow-up could be a persistent lesion from persistent infection with high-risk HPV types or an incident lesion from subsequent infection. Secondly, women infected with HPV 16/18 had the highest risk for persistent CIN. A previous study also suggested that CIN 2 lesions caused by HPV 16 could be less likely to regress than those caused by other high-risk HPV types [1]. Given that women with HPV 16/18 have the highest incidence of CIN 3 and cervical cancer [17, 24, 25], it is expected that HPV 16/18 would have a stronger association with persistence and progression of CIN than other high-risk types; our data were in line with this conception.

We then evaluated whether early HPV testing for high-risk types could identify women whose CIN lesion persisted for 12 months or more. Unfortunately, HPV testing at 6 months

had a sensitivity of 46% in identifying women who had CIN of any severity (≥ CIN 1) at 12 months. In the ASCUS/LSIL Triage Study (ALTS), Guido et al. examined post-colposcopy management strategies for women who had CIN 1 or less determined by histology at initial colposcopy and found that a single HPV testing for high-risk types at 12 months had a sensitivity of 92% in identifying those who had ≥ CIN 2 within 2 years of initial colposcopy [26]. Results from our study and those of ALTS cannot be compared directly because of the differences in length of follow-up, timing of HPV testing, and study outcome (≥ CIN 1 versus ≥ CIN 2, respectively). There were only 22 women who had CIN 2 or CIN 3 at 12 months in our study, and the small number precluded us from examining the sensitivity of HPV testing for detecting ≥ CIN 2 and comparing it with the sensitivity from ALTS. Nevertheless, results from ALTS and our study seem to suggest that HPV testing for high-risk types has a value in identifying women with subsequent CIN 2 or CIN 3 lesions, but it has limited clinical utility if the threshold for CIN detection is CIN 1. ≥ CIN 1 is a less definitive outcome than CIN 2 or CIN 3, because it is an equivocal lesion with a poor reproducibility in its histological diagnosis [8]. Moreover, the association between high-risk HPV types and CIN is stronger in CIN 2 or CIN 3 than in CIN 1 [24]. The difficulty in dichotomizing women into < CIN 1 versus CIN 1 by pathologists as well as the weaker association between CIN 1 and high-risk HPV types dampened down the validity of HPV testing in identifying women with persistence of any lesions when CIN grade was disregarded.

Our study has a few limitations. The majority of initial and endpoint lesions were CIN 1, and we could not examine the value of early HPV testing in detecting CIN 2 or CIN 3 lesions. We did not collect colposcopic images to evaluate whether extent and colposcopic characteristics of the initial lesions could predict CIN outcome. Without colposcopic images, we also could not assess whether the initial and endpoint biopsies were properly directed.

In summary, our results suggest that conservative management of CIN 1 and CIN 2 lesions is safe. When patient compliance is an issue, it is of clinical interest to identify early on those women who are likely to have persistence or progression of CIN and for whom immediate treatment might be considered. Although HPV infection with multiple types, a high-risk type, or HPV 16/18 and persistence of the same high-risk type are significant risk factors for persistent CIN, early post-colposcopy HPV testing for high-risk types at 6 months cannot reliably predict persistence of CIN, if the threshold for detection encompasses the mild and equivocal CIN 1 lesions.

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Table 1

CIN outcome at 12 months by initial CIN status (row percentages shown in parentheses)

	Outcome at 12 months N (%)				
	No lesion	**CIN 1**	**CIN 2**	**CIN 3**	
Study entry					
CIN 1	100 (69.9)	36 (25.2)	5 (3.5)	2 (1.4)	143
CIN 2	34 (54.0)	14 (22.2)	12 (19.0)	3 (4.8)	63
Total	134 (65.0)	50 (24.3)	17 (8.3)	5 (2.4)	206

Table 2

Univariable associations of host and viral factors with persistent CIN at 12 months *

	Persistent CIN/Total (%)	RR (95% CI)	P value†
Baseline Demographic and Lifestyle Factors			
Age			
< 25	28 / 66 (42.4)	1	0.169
25–34	26 / 82 (31.7)	0.75 (0.48 – 1.14)	
≥ 35	18 / 58 (31.0)	0.73 (0.44 – 1.16)	
Race/ethnicity			
Hispanic	49 / 131 (37.4)	1	
Black	18 / 61 (29.5)	0.79 (0.49 – 1.20)	0.298
White	5 / 14 (35.7)	0.95 (0.38 – 1.75)	0.902
Education			
≥ High school	34 / 125 (27.2)	1	
< High school	38 / 81 (46.9)	1.72 (1.19 – 2.51)	0.004
Current smoker			
No	57 / 163 (35.0)	1	
Yes	15 / 43 (34.9)	1.00 (0.60 – 1.52)	0.992
Current use of oral contraceptives			
No	57 / 169 (33.7)	1	
Yes	15 / 37 (40.5)	1.20 (0.73 – 1.81)	0.417
Previous history of CIN			
No	59 / 176 (33.5)	1	
Yes	12 / 28 (42.9)	1.28 (0.74 – 1.96)	0.311
Age of menarche			
≥ 13	31 / 115 (27.0)	1	
< 13	38 / 87 (43.7)	1.61 (1.11 – 2.38)	0.014
Age at first vaginal sex			
> 16	38 / 115 (33.0)	1	
≤16	34 / 90 (37.8)	1.14 (0.78 – 1.66)	0.480
Lifetime # of men for vaginal sex			
0–2	26 / 64 (40.6)	1	0.524
3–4	18 / 64 (28.1)	0.69 (0.41 – 1.12)	
≥ 5	27 / 77 (35.1)	0.86 (0.56 – 1.33)	
# of men for vaginal sex in last 6 months			
0–1	62 / 176 (35.2)	1	
≥ 2	10 / 29 (34.5)	0.98 (0.53 – 1.58)	0.938

	Persistent CIN/Total (%)	RR (95% CI)	P value†
Mean Levels of Mirconutrients over 12 Months			
RBC folate in tertiles (ng/mL)			
Low (≤ 280.1)	20 / 62 (32.3)	1	0.750
Medium (280.2–373.6)	31 / 74 (41.9)	1.30 (0.84 – 2.08)	
High (> 373.6)	21 / 70 (30.0)	0.93 (0.56 – 1.56)	
Plasma levels of reduced ascorbic acid in tertiles (mg/dL)			
Low (≤ 0.45)	28 / 77 (36.4)	1	0.325
Medium (0.46–0.60)	13 / 59 (22.0)	0.61 (0.33 – 1.04)	
High (> 0.60)	31 / 70 (44.3)	1.22 (0.82 – 1.83)	
Baseline Histology Factor			
Abnormal mitosis on initial biopsy			
No	61 / 185 (33.0)	1	
Yes	9 / 15 (60.0)	1.82 (1.03 – 2.69)	0.011
Viral Factors at baseline and over 12 months			
HPV at baseline			
Neg	19 / 65 (29.2)	1	
Pos	50 / 134 (37.3)	1.28 (0.84 – 2.04)	0.274
Proportion of HPV positive visits over 12 months			
0%	9 / 42 (21.4)	1	0.003
1–49%	19 / 60 (31.7)	1.48 (0.77 – 3.13)	
50–74%	5 / 21 (23.8)	1.11 (0.38 – 2.81)	
≥75%	37 / 76 (48.7)	2.27 (1.29 – 4.60)	
# visits seropositive for VLP16 IgG over 12 months			
0	36 / 100 (36.0)	1	0.875
1–3	9 / 32 (28.1)	0.78 (0.39 – 1.36)	
4–5	11 / 27 (40.7)	1.13 (0.63 – 1.83)	

*Total number of subjects may not add up to 206 due to missing questionnaire data at baseline, indeterminate HPV results at a particular visit, or incomplete follow-up.

†For ordinal variables, p values for linear trend are presented.

Table 3

Multivariable associations of host and viral factors with persistent CIN at 12 months

	Adjusted RR (95% CI)	P Value
CIN at study entry		
CIN 1	1	
CIN 2	1.37 (0.97 –1.91)	0.067
Education		
≥ High school	1	
< High school	1.74 (1.22–2.53)	0.003
Proportion of HPV positive visits over 12 months		
0%	1	0.004 *
1–49%	1.45 (0.77–3.04)	
50–74%	1.17 (0.41 – 2.90)	
≥75%	2.16 (1.26 –4.33)	

* P value for linear trend.

Table 4

Multivariable associations of HPV infection with persistent CIN at 12 months [*]

	3-Month Visit		6-Month Visit		9-Month Visit		12-Month Visit	
	Adjusted RR (95% CI)	**P Value[†]**	**Adjusted RR (95% CI)**	**P Value[†]**	**Adjusted RR (95% CI)**	**P Value[†]**	**Adjusted RR (95% CI)**	**P Value[†]**
HPV at visit								
Negative	Reference		Reference		Reference		Reference	
Positive	1.68 (1.08 – 2.74)	0.026	1.75 (1.19 – 2.68)	0.006	1.86 (1.23 – 2.91)	0.004	1.82 (1.25 – 2.72)	0.002
Low-risk type	1.58 (0.85 – 2.79)	0.124	1.37 (0.70 – 2.40)	0.307	1.50 (0.75 – 2.66)	0.195	1.32 (0.67 – 2.29)	0.370
High-risk type	1.74 (1.08 – 2.88)	0.025	1.91 (1.28 – 2.94)	0.002	2.04 (1.32 – 3.25)	0.002	2.09 (1.42 – 3.13)	<.001
Non-16/18 high risk type	1.58 (0.83–2.81)	0.135	1.83 (1.11–2.91)	0.011	1.89 (1.05–3.16)	0.019	2.26 (1.33–3.36)	<.001
HPV 16/18	1.91 (1.07–3.30)	0.020	2.02 (1.23–3.22)	0.003	2.21 (1.33–3.65)	0.002	1.98 (1.25–3.09)	0.002
# HPV types at visit								
Negative	Reference	0.020	Reference	<0.001	Reference	0.001	Reference	0.006
One HPV type	1.55 (0.91–2.64)		1.58 (1.02–2.49)		1.53 (0.88–2.55)		2.08 (1.37–3.04)	
≥ 2 HPV types	1.81 (1.05–3.06)		2.04 (1.19–3.15)		2.17 (1.35–3.52)		1.68 (0.98–2.65)	
Persistent HPV at baseline and follow-up visit[‡]								
(−−) or (+−)	Reference		Reference		Reference		Reference	
(−+) or (+ +) different types	2.34 (1.29 – 3.82)	<.001	1.90 (1.02 – 3.16)	0.023	2.27 (1.52 – 3.56)	<.001	1.62 (0.98 – 2.55)	0.043
(+ +) same low-risk type	1.33 (0.57 – 2.58)	0.440	1.40 (0.66 – 2.49)	0.307	1.32 (0.46 – 2.60)	0.509	1.06 (0.19 – 2.69)	0.928
(+ +) same high-risk type	1.72 (1.03 – 2.90)	0.034	1.83 (1.14 – 2.92)	0.010	1.50 (0.80 – 2.57)	0.161	2.35 (1.57 – 3.55)	<.001
# of HPV positive visits between baseline and follow-up visit[¶]								
0	Reference	0.040	Reference	0.021	Reference	0.007	Reference	0.022
1	1.83 (0.89–4.10)		1.21 (0.51–2.87)		1.51 (0.76–3.24)		1.73 (0.92–3.60)	
2	2.05 (1.11–4.42)		0.85 (0.25–2.35)		1.27 (0.52–2.96)		0.75 (0.22–2.05)	
≥ 3	Not applicable		2.03 (1.11–4.33)		2.16 (1.24–4.35)		2.08 (1.21–4.18)	

[*] RRs were adjusted for CIN grade and education at baseline and estimated using the reference group as indicated.

[†] P values for linear trend are presented for ordinal variables.

[‡]The first and second symbols referred to HPV positivity at baseline and a particular follow-up visit, respectively. For subjects who were HPV positive at both visits, they could have different HPV types at the two visits, or they could have type-specific persistent infection with either the same low-risk or high-risk HPV type.

[¶]There were a maximum of two HPV positive visits between baseline and the 3-month visit, and a maximum of three between baseline and the 6-month visit.

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Table 5

Validity of HPV testing and in combination with cytology and colposcopy results in predicting outcome of CIN at 12 months (95% CI in parentheses)*

	6-month				
Test condition indicating presence of CIN at 12 months	**Sensitivity**	**Specificity**	**Positive predictive value**	**Negative predictive value**	**AUC**
High-risk HPV	45.9 (33.4–58.4)	76.0 (67.8–84.2)	52.8 (39.4–66.3)	70.5 (62.1–79.0)	0.61 (0.53–0.68)
High-risk HPV or cytology ≥ ASC-H	49.2 (36.4–61.9)	68.9 (60.1–77.7)	46.8 (34.4–59.2)	70.9 (62.1–79.7)	0.59 (0.51–0.67)
High-risk HPV or colposcopy +	66.7 (54.4–78.9)	57.3 (47.7–66.8)	46.3 (35.6–57.1)	75.6 (66.1–85.2)	0.62 (0.54–0.70)
High-risk HPV or cytology ≥ ASC-H or colposcopy +	66.7 (54.4–78.9)	53.9 (44.3–63.4)	44.2 (33.7–54.7)	74.7 (64.8–84.5)	0.60 (0.52–0.68)

*ASC-H: Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (HSIL). Colposcopy +: Colposcopic impression of CIN based on the appearance of aceto-white foci and/or both punctation and mosaicism on the cervix.