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The Clinical Meaning of a Cervical Intraepithelial Neoplasia Grade 1 Biopsy

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Abstract

Objective—To determine whether the diagnosis of cervical intraepithelial neoplasia grade 1 (CIN1) increases the risk of cervical intraepithelial neoplasia grade 3 (CIN3) above what is observed for human papillomavirus (HPV) infection.

Methods—Using data from the atypical squamous cells of undetermined significance (ASCUS) and low-grade squamous intraepithelial lesions (LSIL) triage study (ALTS), we compared the 2-year cumulative risk of CIN3 for women with an enrollment diagnosis of CIN1 (n = 594) (median age = 23 years) compared with those with negative histology or no biopsy taken at colposcopy (“no CIN1,” n = 570) (median age = 24 years). Baseline cervical specimens were tested for carcinogenic HPV by a clinical HPV test and HPV genotypes by polymerase chain reaction. Logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI) as a measure of association of enrollment status, including CIN1 compared with no CIN1 diagnosis, with 2-year worst outcomes of CIN3.

Results—The two-year risks of CIN3 were 10.3% (95%CI: 7.9%–13.0%) for women with CIN1, 7.3% (95%CI: 4.6%–10.9%) for negative histology, and 6.4% (95%CI: 3.8%–9.9%) for women referred to colposcopy and no biopsies were taken (p = 0.1). The 2-year risk of CIN3 for women positive for HPV16, HPV18, or other carcinogenic HPV genotypes was 19.1%, 13.9%, and 5.7%, respectively, and did not differ significantly by the baseline cytology interpretation (ASCUS or LSIL). Taking HPV genotypes into account, having a CIN1 (compared with no CIN1) was not a risk factor for developing CIN3 (OR = 0.99, 95%CI: 0.54–1.8).

Conclusions—A CIN1 diagnosis does not represent a significant risk factor for CIN3 above the risk attributed to its molecular cause, genotype-specific HPV infection.

Introduction

Cervical intraepithelial neoplasia grade 1 (CIN1) is the most common histologic biopsy diagnosis following referral for colposcopy for a positive cervical cancer-screening test. Although CIN1 is recognized as primarily the histologic manifestation of a human

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papillomavirus (HPV) infection, CIN1 is often (incorrectly) grouped with more severe grades, CIN2 and CIN3, as “CIN” or cervical neoplasia, implying precancer. In part, this is due to the diagnostic challenge of distinguishing CIN1 from CIN2 and from negative histology reproducibly (1;2).

Yet, the clinical implications of CIN1 are not well understood as there are few contemporary prospective studies to explore the subsequent risk of cervical precancer. An earlier review suggested that 10% of women with CIN1 develop CIN3 in the next 10 years (3). In the atypical squamous cells of undetermined significance (ASCUS) and low-grade squamous intraepithelial lesion (LSIL) triage study (ALTS), the two-year risk of CIN3 was 9% (4). Other studies have found lower risks. For example, a randomized trial for the management of CIN1 found that 4.4% of women with CIN1 were diagnosed with CIN2/3 in 18 months (5). An analysis of 1,001 CIN1 found that 7% were diagnosed with CIN2/3 at the 6 month follow-up (6). The widely variable risks between studies may be due to many factors, including diagnostic errors, differences in diagnostic thresholds for each CIN category, population differences, the follow-up protocol, and the time of follow-up.

Now that HPV infection is known to be the causal agent underlying cervical carcinogenesis, we have become interested in the meaning of histologic CIN1 diagnoses compared with not finding CIN1 (i.e., negative biopsies or no biopsies taken due to normal colposcopic impressions). Taking HPV infection status into account, does finding CIN1 imply greater risk of CIN3 than not finding it? We therefore conducted a retrospective study of primarily younger (younger than 30 years) women diagnosed with CIN1 at enrollment of ALTS as a follow-up of a previous study (4).

Methods

Study Design and Population

ALTS (1997–2001) was a multi-site, randomized clinical trial comparing three management strategies (Immediate Colposcopy [IC], HPV Triage, or Conservative Management [CM]) for women referred for ASCUS (n = 3,488) or LSIL (n = 1,572) conventional cytology (9–13). “ASCUS” under the 1991 Bethesda system (7) was slightly more inclusive, particularly of probable reactive changes and ASC-H (atypical squamous cells, cannot rule out high-grade intraepithelial lesion), than the “ASC-US” category of the 2001 Bethesda system (8). The National Cancer Institute and local institutional review boards approved the study and all participants provided written, informed consent.

At enrollment and follow-up visits over the two-year duration, all women underwent a pelvic examination with collection of two cervical specimens. The first specimen in PreservCyt for ThinPrep cytology (Hologic, Bedford, MA, USA) and clinical HPV testing by Hybrid Capture 2 (a clinical HPV test); Qiagen, Gaithersburg, MD) and the second in specimen transport medium (STM; Qiagen, Gaithersburg, MD, USA). Women in all three arms of the study were reevaluated by cytology every six months during the two years and sent to colposcopy if cytology was high-grade squamous intraepithelial lesion (HSIL). An exit examination with colposcopy was scheduled for all women. We refer readers to other references for details on randomization, examination procedures, patient management, and laboratory and pathology methods (9–13).

We used diagnoses by clinical center (CC) pathologists to establish the baseline histologic status (CIN1, negative histology, or no biopsy). We restricted our analysis to women randomized to the IC or HPV Triage arms and either referred to colposcopy for an ASCUS Pap test and testing HC2 positive (HPV-positive ASCUS) or for an LSIL Pap test to better reflect the current practice of referral to colposcopy (14). We note that in the HPV Triage

arm, a small proportion of women referred with a LSIL Pap test were not included in this analysis because they tested HPV negative by HC2 (33 of 224 [14.7%] in the HPV Triage Arm) at enrollment. In contrast, current guidelines recommend that all women with LSIL, regardless of HPV status, undergo colposcopy (14). We excluded CIN1 in the CM study arm because women in this arm were only referred to colposcopy if they had enrollment HSIL cytology.

There were 738 women with enrollment biopsies diagnosed as CIN1 (including 16 women with missing data on whether a biopsy was taken and 10 who had a baseline diagnosis of CIN1 but no biopsy data recorded), 346 diagnosed as negative by the clinical center pathologists, and 346 who went to colposcopy but had histologic outcome (including 17 women with missing data on whether a biopsy was taken). This analysis was further restricted to those women who were exited from the study, i.e., those who had an exit visit at 24 months or were treated and censored from the study: 594 (80.5%) with CIN1, 289 (83.5%) with negative histology, and 281 (81.2%) with no biopsy. There was no significant difference in the % of women exited from the study ($p = 0.5$, Fisher's exact test) by biopsy outcome. Over the 2-year duration of ALTS, the quality control pathology group (QC pathology) diagnosed 100 women with CIN3, which was the primary endpoint for this analysis. We also used an endpoint of CIN2/3 ($n = 138$) as diagnosed by the clinical center pathologists (CC pathology) as it is relevant to clinical practice since these women would be treated according to current management guidelines (15).

HPV Testing

HC2, a DNA test that targets (with some cross-reactivity for other types) a pool of 13 carcinogenic HPV genotypes (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68), was performed on residual PreservCyt specimens as previously described (16). STM specimens were tested for 27 or 38 HPV genotypes using a PCR assay, line blot assay (LBA; Roche Molecular Systems, Pleasanton, CA, USA), as previously described (14;17). We used the HPV16 and HPV18 results from LBA among the HC2 positives to mimic currently available tests that offer HPV16 and HPV18 genotyping and classify women hierarchically according to established cancer risk (HPV risk group or status) (18): HPV16 positive, else HPV16 negative and positive for HPV18, else negative for HPV16 and HPV18 but positive for the other carcinogenic HPV genotypes as measured by HC2, or else negative for all carcinogenic HPV genotypes and positive for non-carcinogenic HPV genotypes or HPV negative (HPV16>HPV18>other carcinogenic HPV>non-carcinogenic/HPV negative). Four women with no biopsy, 6 women with a negative biopsy, and 20 women with CIN1 were missing HPV results.

Statistical Analysis

The enrollment characteristics for women with CIN1, negative histology, or no biopsy were compared and tested for statistical significance using Pearson's chi-square tests. We calculated the two-year risk of QC pathology CIN3 and CC pathology CIN2/3, overall and stratified by baseline status (CIN1, negative histology, or no biopsy), relevant screening results (e.g., referral Pap and HC2 results), and HPV risk group. Fisher's exact or a Pearson's chi-square tests as appropriate were used to test for statistical differences in risk. Binomial exact 95% confidence intervals (95%CI) were calculated for CIN3 risks where noted.

Finally, we used logistic regression (19) to calculate odds ratios (OR) and 95%CI to model the association of risk factors with QC pathology CIN3 and CC pathology CIN2/3. P values of <0.05 were considered statistically significant. STATA 11.0 (STATA Corporation, College Station, TX) was used for analyses.

Results

There were statistically significant but slight differences in the age at enrollment for women with CIN1, negative histology, or no biopsy (median age of 23 years, 24 years, and 23 years, respectively, $p = 0.04$). A comparison of the study and behavior characteristics between these three populations is shown in Table 1. There were significant differences between the three groups for some study characteristics: the enrolling clinical center and the referral Pap. Women with CIN1 were more likely to be classified as having riskier HPV genotypes ($p = 0.02$) and were more likely to have a smoking history ($p = 0.02$) than the other groups. There was no significant difference between groups by race, ever being pregnant, or oral contraceptive use (data not shown). Comparing negative histology to women without a biopsy, the only differences between the two groups were the enrolling clinical center ($p < 0.001$). There were significant differences ($p < 0.001$) in the distribution of colposcopic impressions between the three groups, with 86.5% of CIN1 and 90.0% of negative histology having a low-grade colposcopic impression or more severe whereas 81.3% of women with no biopsy had a completely normal colposcopic impression.

The two-year risks of CIN3 were 10.3% (95% CI: 7.9–13.0%) for women with CIN1, 7.3% (95% CI: 4.6–10.9%) for negative histology, and 6.4% (95% CI: 3.8–9.9%) for women referred to colposcopy and no biopsies were taken ($p = 0.1$) (Table 2). There were no obvious patterns or trends in the small differences in the CIN3 risk between women referred for an ASCUS Pap and tested HPV positive compared to a LSIL Pap. Most women referred for a LSIL Pap and being diagnosed with CIN1, negative histology, or no biopsy taken tested HC2 positive (90.2%, 85.6%, or 80.9%, respectively).

We also present the risks following referral ASCUS and LSIL Pap tests for women randomized to the IC arm as an unbiased reference; we noted that there were no appreciable differences in the risks following a LSIL Pap test for the IC and HPV arms vs. IC alone, despite the per protocol exclusion of the women with HPV-negative LSIL from undergoing colposcopy in the HPV study arm. Because there was no statistical difference in the overall two-year risk of CIN3 ($p = 0.7$) and CIN2/3 ($p = 0.7$) between women with negative histology and no biopsy, for greater power, we combined the two groups in the subsequent analyses into a single group (“no CIN1”) ($n = 570$), with a two-year risk of CIN3 of 6.8% (95% CI: 4.9–9.2).

In the initial analysis that did not take HPV status into account, women with a CIN1 diagnosis were non-significantly more likely to have an enrollment high-grade cytology (HSIL or atypical squamous cells cannot rule out HSIL) than women with no CIN1, 8.0% vs. 5.8% ($p = 0.2$). Among women with CIN1, those having an enrollment high-grade cytology were at twice the risk of CIN3 compared to women without an enrollment high-grade cytology (19.2% vs. 9.6%, respectively, $p = 0.05$). Among women with no CIN1, those having an enrollment high-grade cytology were also at approximately twice the risk of CIN3 compared to women without an enrollment high-grade cytology (12.1% vs. 6.6%, respectively, $p = 0.2$), albeit at a lower absolute level.

Before HPV status was considered, the risk of CIN3 (vs. no CIN3) was greater ($p = 0.04$) for those with CIN1 than those from those with no CIN1 at enrollment. Stratified by HPV risk group status (Table 3), there was a gradient of risk for CIN3 according to the HPV risk group ($p_{\text{trend}} < 0.0001$; (20)): 19.1% (95% CI: 13.1%–25.3%) for HPV16 positives, 13.9% (95% CI: 7.2%–23.5%) for HPV18 positives, 5.7% (95% CI: 4.2%–7.6%) for HC2 positives (HPV16/18 negative), and 5.2% (95% CI: 1.1%–14.4%) for HC2 negatives. There was no statistically significant difference in the two-year risk of CIN3 by baseline histology status stratified by HPV risk group and relevant screening result (HC2-positive ASCUS or LSIL),

although no CIN1 tended to have slightly lower risks than CIN1. Similar patterns were observed for the clinical center pathology endpoint of CIN2/3.

Finally, we examined the relationship of enrollment characteristics, notably including HPV status, and the two-year risk of CIN3 using a logistic regression model that considered CIN3 and CIN2 as distinct endpoints (Table 4). Being HPV16 positive (OR = 3.2, 95% CI = 1.6–6.7) (vs. HC2 positive and HPV16/18 negative) and having an enrollment high-grade cytology (high-grade squamous intraepithelial lesion (HSIL) or atypical squamous cells, cannot rule out HSIL)(OR = 2.4, 95% CI = 1.2–4.9) (vs. less severe high-grade cytology) were independently associated with an elevated CIN3 risk. Being HPV18 positive (OR = 1.2, 95% CI 0.26–5.5) was not independently associated with CIN3. Enrollment CIN1 (vs. no CIN1) (OR = 0.99, 95% CI 0.54–1.8) was not associated with CIN3. Similar associations were observed for the CC pathology endpoint of CIN2/3 (data not shown).

Other enrollment variables, including the number of biopsies taken at enrollment, and number of HPV genotypes, were not associated with CIN3 or CIN2 (data not shown). When added to the model, non-normal colposcopic impression did not significantly predict CIN3 or CIN2 compared to a normal colposcopic impression (data not shown).

Excluding those women with baseline histology was upgraded to CIN3 by QC pathology (18 cases from CIN1 and 4 cases from no CIN1), perhaps due to misclassification, the two-year risks of CIN3 were 7.5% and 6.2% ($p = 0.2$) following CIN1 and no CIN1 diagnosis, respectively. The results of the logistic regression did not appreciably change when we excluded the aforementioned cases (data not shown).

Discussion

Here, we examined whether having a diagnosis of CIN1 represented an independent risk factor above HPV infection alone for the development of incident CIN3. After controlling for HPV risk group and the presence of enrollment high-grade cytology, we found no evidence that having CIN1 significantly elevated the two-year risk of incident CIN3 compared to negative histology or colposcopically normal women. Thus, differences in two-year risk of CIN3 between CIN1 and negative histology or no biopsy were primarily due to differences in the distribution in HPV genotypes and the fraction of women with enrollment CIN3 missed by colposcopically directed biopsy but indicated by concurrent (enrollment) high-grade cytology. Thus, etiologically, HPV genotype is the primary cause of CIN3 rather than the distinction between CIN1 and no CIN1.

From a clinical perspective, women with CIN1 had a 10% two-year risk of CIN3 compared to 7% for negative histology and 6% for no biopsy, statistically significant but small absolute risk differences. Given the general similarities in risk, these outcomes of screening might be managed similarly(21). That is, given that there are a limited number of management options (routine screening, increased surveillance, or follow-up colposcopy) and the general similarities in risk, it might difficult to justify differential management by histologic status in this population, depending on the accepted thresholds of risk for each management option. We note that the risks of CIN3 reported here were similar to the previous analysis on CIN1 from ALTS (4).

Having HPV16- or HPV18-positive CIN1 or no CIN1 elevated the two-year risk 3-fold and 2-fold, respectively, compared testing positive by HC2 for other carcinogenic HPV genotypes. Similar patterns were observed when using CC pathology diagnosis of CIN2/3 as the endpoint: women positive for HPV16 (19.9%) and HPV18 (16.1%) were at an elevated risk compared to those positive for other, non-HPV16/18 carcinogenic HPV genotypes (10.3%) ($p = 0.002$).

All 13 cases of CIN3 in the HC2-negative group tested negative for any carcinogenic HPV genotype and 10 of 13 tested negative for all HPV genotypes by PCR. This suggests some of these CIN3 following a HC2-negative result developed from newly acquired HPV infections after enrollment or were misclassified by the QC pathology group; fewer QC-pathology diagnosed CIN3 were confirmed by the CC pathologists following a HC2-negative versus a HC2-positive result (17.5% vs. 51.5%, respectively, $p = 0.04$).

We note several additional limitations in our analysis: 1) We had a limited number of CIN3 diagnosed, limiting our ability to provide more precise measures of CIN3 risk; 2) Our population was relatively young and therefore is not representative of older women who are diagnosed with CIN1, negative, or no histology. We did not find that age was associated with risk of CIN3 (data not shown) but we had only approximately 20% who were 30 and older, and 5% who were 40 and older. Therefore these data do not inform about the appropriate management of women with CIN1; 3) We did not have longer-term follow-up of these women to determine the outcomes of all infections and associated histopathology. HPV-positive women remain at risk of CIN3 or cancer for many years, at least until there is molecular evidence of clearance (22); 4) Although all women exiting ALTS received colposcopy, almost certainly some CIN3 was missed due to limitations in sensitivity of colposcopy to find disease, especially when only a single colposcopically directed biopsy that was the common practice at the time of ALTS (23;24); 5) Women with a high-grade Pap were not referred into ALTS and therefore we cannot generalize our findings to all women with these colposcopy and biopsy results. It seems likely that women referred for a high-grade Pap would be a greater risk of CIN3 than women with less severe cytologic abnormalities due to their a priori risk. Indeed, we observed that the women who had an enrollment HSIL cytology were more likely to develop CIN3; and 6) a small fraction of women were referred into ALTS and had LSIL were not included in this analysis because they were randomized to the HPV arm and they tested HPV negative. We would expect women with HPV-negative LSIL and a histologic diagnosis of $\leq$ CIN1 to have a lower risk than the HPV-positive LSIL counterpart. Thus we may have slightly overestimated the CIN3 risk following a LSIL Pap and $\leq$ CIN1 histology compared to women who would be referred to colposcopy with LSIL in current clinical practice although we did not observe a qualitative difference in risk for the women with a LSIL Pap in the IC arm, which includes all HPV-negative and HPV-positive women, versus those in the HPV.

The strength of the study is the use of consensus CIN3 diagnosis as the primary endpoint rather than CIN2/3. Previous studies have shown that CIN2 is an equivocal diagnosis of precancer(2) and more importantly in this context that CIN2 has very poor inter-rater agreement (1;2) and is much more likely to regress (25;26) than CIN3. Therefore the risks of CIN2/3 are more apt to vary depending on who is making the diagnosis and what is the follow-up protocol, respectively, making comparisons of risks between studies that included CIN2 as an endpoint challenging to interpret. We did include the clinical center pathology diagnosis of CIN2/3 to show that the general patterns of risk and determinants were nevertheless the same as for QC pathology CIN3.

In conclusion, we found nothing intrinsic in the diagnosis of CIN1 that significantly elevated the two-year risk of CIN3+ above the molecular cause of the CIN1, HPV infection. Women who were diagnosed with CIN1 were more likely to have HPV16, which in turn increased the risk of CIN3. This is perhaps not unexpected since HPV16-positive cervical lesions are more apparent to colposcopists than lesions caused by other HPV genotypes (27), naturally leading to a bias as to where biopsies were taken and therefore identifying women with HPV16-positive CIN1. Although the risk differences between HPV16-positive and HPV16-negative (or HPV18-positive or HPV18 negative) CIN1 or no CIN1 may not be sufficiently different to offer differential clinical management of patients, when valid testing of HPV16

results are presented in this context, doctors should be cognizant that HPV16-positive (and HPV18-positive) women are at an elevated risk of CIN3 in the subsequent few years. Finally, categorizing histologic diagnoses as “CIN” is a gross misclassification of disease since CIN1, CIN2, and CIN3 represent different biological entities and their associated cancer risks differ greatly.

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Characteristics of Women With No Biopsy at Enrollment, an Enrollment Clinical Center Diagnosis of Negative Histology, or Diagnosis of Cervical Intraepithelial Neoplasia Grade 1

Table 1

Study arm	No Biopsy (n = 281)		Negative Histology (n = 289)		CIN1 (n = 594)		P*	P†
	n	%	n	%	n	%		
Immediate colposcopy	166	59.1%	181	62.6%	384	64.6%	0.3	0.4
HPV testing	115	40.9%	108	37.4%	210	35.4%		
Center								
1	114	40.6%	103	35.6%	270	45.5%	<0.001	<0.001
2	64	22.8%	31	10.7%	86	14.5%		
3	37	13.2%	42	14.5%	108	18.2%		
4	66	23.5%	113	39.1%	130	21.9%		
Referral Pap								
ASCUS	188	66.9%	186	64.4%	300	50.5%	<0.001	0.5
LSIL	93	33.1%	103	35.6%	324	54.5%		
HPV status								
HPV negative or noncarcinogenic	75	26.7%	68	23.5%	112	18.9%	0.02	0.08
Carcinogenic	153	54.4%	183	63.3%	376	63.3%		
HPV16	53	18.9%	37	12.8%	196	33.0%		
Missing	0	0.0%	1	0.3%	0	0.0%		
Smoking status								
Never	173	61.6%	163	56.4%	323	54.4%	0.02	0.2
Former	35	12.5%	34	11.8%	51	8.6%		
Current, less than one pack per day	61	21.7%	66	22.8%	150	25.3%		
Current, one or more packs per day	12	4.3%	25	8.7%	67	11.3%		
Missing	0	0.0%	1	0.3%	3	0.5%		

CIN1, cervical intraepithelial neoplasia grade 1; HPV, human papillomavirus; ASCUS, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesions.

* Differences between all groups (Pearson chi-square)

† Differences between no biopsy and negative histology (Pearson chi-square)

Pearson chi-square tests were used to test for differences between the groups.

Table 2

Two-Year Risk of Cervical Intraepithelial Neoplasia (CIN) Grade 3 as Diagnosed by the Quality Control Pathology Group After an Enrollment Diagnosis of CIN Grade 1 or Negative Histology on Biopsy by the Clinical Center Pathologists, or After No Biopsy Was Taken

	n	n _{CIN3}	%CIN3	95%CI
CIN1				
All	594	61	10.3%	7.9–13.0%
HPV-positive ASCUS	300	24	8.0%	5.2–11.7%
LSIL	294	37	12.6%	9.0–16.9%
ASCUS*	244	18	7.4%	4.4–11.4%
LSIL*	238	32	13.4%	9.4–18.4%
Negative histology				
All	289	21	7.3%	4.6–10.9%
HPV-positive ASCUS	186	16	8.6%	5.0–13.6%
LSIL	103	5	4.9%	1.5–10.7%
ASCUS*	259	12	4.6%	2.4–8.0%
LSIL*	81	4	4.9%	1.4–12.2%
No biopsy				
All	281	18	6.4%	3.8–9.9%
HPV-positive ASCUS	188	10	5.3%	2.6–9.6%
LSIL	93	8	8.6%	3.8–16.2%
ASCUS*	268	11	4.1%	2.0–7.2%
LSIL*	64	5	7.8%	2.6–17.3%
Less than CIN1 (negative histology and no biopsy)				
All	570	39	6.8%	4.9–9.2%
HPV-positive ASCUS	374	26	7.0%	4.6–10.0%
LSIL	570	39	6.8%	3.6–11.1%
ASCUS*	196	13	6.6%	3.6–11.1%
LSIL*	145	9	6.2%	2.9–11.5%

CIN3, cervical intraepithelial grade 3; CI, confidence interval; HPV, human papillomavirus; HPV-positive, positive for carcinogenic HPV; ASCUS, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesions.

Binomial exact 95% confidence intervals (95%CI) are provided. The risks are shown for all women within a group and for subsets of women with different screening outcomes. The analysis was restricted to women referred for an ASCUS Pap and testing HPV positive.

* Women in the immediate colposcopy arm only

Two-Year Risks of Cervical Intraepithelial Neoplasia (CIN) Grade 3 as Diagnosed by the Quality Control Pathology Group for Women, or CIN Grade 2/3 as Diagnosed by the Clinical Center (CC) Pathologists After an Enrollment Diagnosis of No CIN or CIN Grade 1 by the CC Pathologists*

Table 3

Histology	Cytology	n	End Point	HPV16		HPV18		Carcinogenic HPV-Positive		Carcinogenic HPV-Negative	
				n = 194	%Risk	n = 79	%Risk	n = 803	%Risk	n = 58	%Risk
All	All	1134	QC CIN3	19.1%	13.9%			5.7%		5.2%	
			CC CIN2/3	20.1%	16.5%			9.7%		8.6%	
	HPV-positive ASCUS	674	QC CIN3	15.5%	15.0%			4.9%		n/a	
			CC CIN2/3	18.7%	15.0%			9.4%		n/a	
	LSIL	460	QC CIN3	25.4%	12.8%			7.2%		5.2%	
			CC CIN2/3	22.5%	18.0%			10.3%		8.6%	
CIN1	All	574	QC CIN3	22.1%	17.7%			6.1%		7.4%	
			CC CIN2/3	21.2%	19.6%			10.7%		11.1%	
	HPV-positive ASCUS	300	QC CIN3	16.1%	17.4%			5.0%		n/a	
			CC CIN2/3	19.6%	17.4%			10.4%		n/a	
	LSIL	274	QC CIN3	29.2%	17.9%			7.6%		7.4%	
			CC CIN2/3	22.9%	21.4%			11.1%		11.1%	
Less than CIN1	All	560	QC CIN3	15.6%	7.1%			5.4%		3.2%	
			CC CIN2/3	18.9%	10.7%			8.8%		6.5%	
	HPV-positive ASCUS	374	QC CIN3	14.9%	11.8%			4.8%		n/a	
			CC CIN2/3	17.9%	11.8%			8.6%		n/a	
	LSIL	186	QC CIN3	17.4%	0.0%			6.6%		3.2%	
			CC CIN2/3	21.7%	9.1%			9.1%		6.5%	

HPV, human papillomavirus; HPV-positive, positive for carcinogenic HPV. QC, quality control; CIN3, cervical intraepithelial neoplasia grade 3; ASCUS, atypical squamous cells of undetermined significance; CIN 2/3, cervical intraepithelial grade 2/3; LSIL, low-grade squamous intraepithelial lesions.

* Stratified by hierarchically classified human papillomavirus risk group: HPV 16 positive; else HPV16 negative and HPV18 positive; else HPV16 and HPV18 negative and carcinogenic HPV positive; else carcinogenic HPV negative.

Table 4

Association of Enrollment Characteristics With a 2-Year Quality Control Pathology Group Diagnosis of Cervical Intraepithelial Neoplasia (CIN) Grade 3, or 2-Year Clinical Center (CC) Pathology Diagnosis of CIN Grade 2/3 After an Enrollment Diagnosis of No CIN1 or CIN1 by the CC Pathologists*

	QC CIN3				CC CIN2/3			
	OR	LL	UL	OR	LL	UL	OR	LL
Histology								
<CIN1	1.0	-----		1.0		-----		
CIN1	0.99	0.54	1.8	1.2	0.76	2.0		
HPV status [†]								
Carcinogenic HPV Negative	0.47	0.060	3.7	0.75	0.17	3.4		
Carcinogenic HPV Positive	1.0	-----		1.0	-----			
HPV18	1.2	0.26	5.5	1.2	0.34	4.2		
HPV16	3.2	1.6	6.7	2.3	1.2	4.4		
Enrollment cytology status								
less than high-grade	1.0	-----		1.0	-----			
high-grade	2.4	1.2	4.9	1.9	0.99	3.5		
Referral Pap test								
ASCUS	1.0	-----		1.0	-----			
LSIL	1.5	0.92	2.3	0.8	0.69	1.5		
Center								
1	1.0	-----		1.0	-----			
2	0.73	0.38	1.4	1.3	0.74	2.2		
3	1.0	0.56	1.9	1.0	0.57	1.7		
4	0.58	0.32	1.1	0.9	0.52	1.4		
Smoking								
Never	1.0	-----		1.0	-----			
Former	1.4	0.69	2.9	1.7	1.0	3.1		
Current, less than one pack per day	1.3	0.76	2.2	1.4	0.89	2.2		
Current, one or more packs per day	1.6	0.81	3.2	1.6	0.89	2.9		

CIN 2/3, cervical intraepithelial grade 2/3; CIN 3, cervical intraepithelial grade 3; QC, quality control; OR, odds ratio; LL, low limit of 95% confidence interval; UL, upper limit of 95% confidence interval; HPV, human papillomavirus; ASCUS, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesions.

* Results of a logistic regression model.

[†] Hierarchically classified human papillomavirus risk group: HPV 16 positive; else HPV 16 negative and HPV 18 negative and carcinogenic HPV positive; else carcinogenic HPV negative.

High-grade cytology was defined as having a cytologic interpretation of high-grade squamous intraepithelial lesions (HSIL) or atypical squamous cell, cannot rule out HSIL at enrollment. Bolded type indicates a statistically significant ($P < 0.05$) association with either endpoint.