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Evidence for Frequent Regression of Cervical Intraepithelial Neoplasia-Grade 2

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Abstract

Objective—To estimate the fraction of cervical intraepithelial neoplasia-2 (CIN-2) that might regress if untreated using data from the atypical squamous cells of undetermined significance (ASCUS) and low-grade squamous intraepithelial lesions (LSIL) triage study (ALTS).

Methods—We compared the cumulative occurrence of CIN-2 ($n = 397$) and CIN-3 or worse ($n = 542$) diagnosed by the Pathology Quality Control Group in three trial arms— immediate colposcopy, human papillomavirus (HPV) triage, and conservative management— over the 2-year duration of the ALTS trial. A non-parametric test of trend was used to test for differences in the number of CIN-2 cases relative to number of CIN-3 or worse cases across study arms, with an increasing percentage of women referred to colposcopy at baseline.

Results—There were no significant differences in the cumulative 2-year cumulative CIN-3 or worse diagnoses by study arm (10.9%, conservative management; 10.3%, HPV; 10.9%, immediate colposcopy) ($p_{\text{trend}} = 0.8$) but there was a significant increase in CIN-2 diagnoses (5.8%, conservative management; 7.8%, HPV triage; 9.9%, immediate colposcopy) ($p_{\text{trend}} < 0.001$) in the study arms with increasing number of women referred to colposcopy at baseline. The relative differences in CIN-2 by study arm among women who tested HPV16 positive at baseline were less pronounced ($p_{\text{trend}} = 0.1$) than women who tested positive for other high-risk HPV genotypes ($p_{\text{trend}} = 0.01$).

Conclusions—There was evidence that approximately 40% of undiagnosed CIN-2 will regress over 2 years but CIN-2 caused by HPV16 may be less likely to regress than CIN-2 caused by other high-risk HPV genotypes.

Introduction

In cervical cancer screening programs, women are sent to colposcopy for a diagnostic evaluation and biopsy of evident lesions if they screen positive by cytology or, increasingly, by various combinations of cytology and human papillomavirus (HPV) test results (1). Women diagnosed with a high-grade cervical lesion, defined in the U.S. as cervical intraepithelial neoplasia grade 2 (CIN2) or worse, are then treated, primarily by excision. However, there is increasing awareness that not all CIN3 (2) and especially not all CIN2 is “precancer” (3). In fact, a large proportion of CIN2 lesions may resolve without treatment, leading to

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recommendations not to treat CIN2 immediately in young women (4). The natural history of CIN2 is not clear, partly because most recent studies that have examined regression of histologically-confirmed high-grade lesions did not differentiate between CIN2 and CIN3 diagnoses, had sample sizes of ≤ 100 cases (5), and did not employ rigorous pathology review to rule out misclassification of CIN1 and CIN2.

To examine the specific issue of CIN2 regression, data from the atypical squamous cells of undetermined significance (ASCUS) and low-grade squamous intraepithelial lesion (LSIL) triage study (ALTS) were used. Different algorithms for referring women to colposcopy at baseline in ALTS were used analytically to compare how the aggressiveness of referral to colposcopy influenced the cumulative 2-year incidence of CIN2.

Methods

ALTS was a multi-site, randomized trial comparing three management strategies for women referred for ASCUS ($n = 3,488$) or LSIL ($n = 1,572$) conventional cytology (6–10). The arms were: 1) immediate colposcopy (IC arm) (referral to colposcopy regardless of enrollment test results); 2) HPV triage (HPV arm) (referral to colposcopy if the enrollment HPV result was positive by Hybrid Capture 2 (hc2; Qiagen Corporation, Gaithersburg, MD) or missing, or if the enrollment cytology was high-grade squamous intraepithelial lesion [HSIL]); or 3) conservative management (CM arm) (referral to colposcopy only if the enrollment cytology was HSIL). Among women with LSIL randomized to the CM arm ($n = 675$), seven women (1.0%) during enrollment and 136 women (20.1%) during follow-up were sent to colposcopy on the basis of a protocol modification initiated as a safety intervention (8); if this happened to be the 18-month follow-up visit and colposcopy was performed, the 18-month visit became the participant's "exit" visit (see below).

At enrollment, all women received a pelvic examination with collection of two cervical specimens; the first specimen in PreservCyt for ThinPrep cytology (Cytoc Corporation, Marlborough, MA, USA) and hc2 pooled testing (Qiagen Corporation) and the second in specimen transport medium (STM; Qiagen Corporation) for HPV genotyping. Women in the three arms of the study were re-evaluated by cytology every 6 months for 2 years of follow-up and sent to colposcopy if cytology was HSIL. A CIN2 or worse ($\geq$ CIN2) diagnosis by the clinical center pathologists was the treatment threshold. An exit examination with colposcopy was scheduled for all women, with loop electrosurgical excision offered for $\geq$ CIN2 or persistent low-grade lesions. The National Cancer Institute and local institutional review boards approved the study and all participants provided written informed consent.

Clinical management was based on the clinical center pathologists' cytologic interpretations and histologic diagnoses as previously described (6–10). Referral smears, ThinPreps, and histology slides were also sent to the Pathology Quality Control Group (QC Pathology) based at the Johns Hopkins Hospital for review, including computer-assisted review, and secondary diagnoses as previously described (6–10).

Two HPV DNA tests were performed on clinical specimens collected at enrollment. Hybrid Capture 2 using probe set B, a pooled probe DNA test for one or more carcinogenic or high-risk (HR)-HPV genotypes (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68), was performed on PreservCyt specimens (10). A positive test does not identify which HR HPV genotype(s) are present. Hybrid Capture 2 is also well-known to cross-react with untargeted HPV genotypes (11;12), including HPV66, recently classified as a HR-HPV genotype(13). A L1 consensus primer-based PCR assay (14;15) was performed on the STM specimen to test for 27 or 38 HPV genotypes.

HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 were considered primary HR HPV genotypes. An *a priori* HPV risk grouping was established according to cervical cancer risk as follows: 1) positive for HPV16; 2) HPV16 negative, but positive for other HR HPV genotypes by PCR or by hc2 if PCR was negative or missing; 3) negative for all HR HPV genotypes but positive for non-HR HPV genotypes (n.b., specimens that tested positive for non-HR HPV by PCR and positive by hc2 were conservatively called non-HR HPV positive because hc2 sometimes cross-reacts with non-HR HPV genotypes (11;12); or 4) PCR negative.

We used the worst histological diagnosis by the Pathology Quality Control Group (QC Pathology) over the 2-year duration of ALTS for these analyses. In order to measure the regression of CIN2 (n = 397), we relied on the fact that different study arms of ALTS were less or more aggressive in colposcopic referral and detection of CIN2 or worse ($\geq$ CIN2): The CM arm sent 188 of 1839 women (10.2%), the HPV arm sent 768 of 1385 women (55.5%), and the IC arm sent 1317 of 1836 women (99.0%) women to colposcopy at enrollment (8;9). Forty women in the HPV arm, 1 with CIN2 and 6 with CIN3, were referred to colposcopy because of missing hc2 results. We used CIN3 or worse ($\geq$ CIN3) (n = 542; 535 CIN3 and 7 cancers) diagnoses as a reference group under the assumptions that 1) CIN3 was much less likely to regress than CIN2 and 2) the majority of $\geq$ CIN3 diagnosed, regardless of the timing of the diagnosis, was already present at the time of enrollment.

An extension of the Wilcoxon rank-sum test was used as a non-parametric test for trend across study arms (16). Binomial exact confidence intervals were calculated for proportions. A P value < 0.05 was considered statistically significant. Stata version 8.2 (Stata Corporation, College Station, TX) was used for all statistical analyses.

Results

We included in our analysis the 5,052 of 5,060 women (99.8%) for whom we had HPV data (hc2 and/or PCR). Table 1 shows the demographics and risk factors for women by their worst 2-year histologic diagnosis (<CIN2, CIN2, or $\geq$ CIN3) as rendered by QC Pathology. As previously noted, smokers (vs. non-smokers)(17) and the less educated (18) were more likely to be diagnosed with $\geq$ CIN3.

Table 2 shows that there was little difference ($p_{\text{trend}} = 0.8$) in the proportion of women diagnosed with $\geq$ CIN3 over the two year duration of ALTS in the populations randomized to each study arm (10.9%, 10.3%, and 10.9% in the CM, HPV, and IC arms, respectively). However, the proportion of women diagnosed with CIN2 differed by study arm: 5.8% (95% CI = 4.7%–6.9%) in the CM arm, 7.8% (95% CI = 6.5%–9.4%) in the HPV arm, and 9.9% (95% CI = 8.6%–11.4%) in the IC arm. That is, there were more diagnoses of CIN2 with strategies referring larger proportions of women to baseline colposcopy in the trial (CM<HPV<IC), with 41.6% (95% CI = 24.3%–59.0%) fewer cases of CIN2 diagnosed in the CM arm compared to the IC arm. Given that follow-up and exit screening and management did not differ by study arm, the differences in proportion of women diagnosed with CIN2 by the study arm were due to the differences in the number of women sent to colposcopy at baseline in each study arm. There was a significant trend ($p_{\text{trend}} < 0.001$) of fewer two-year cumulative CIN2 histologic diagnoses by study arm relative to two-year cumulative $\geq$ CIN3. Exclusion of women in the CM, referred for a LSIL Pap, and sent for an early colposcopic evaluation for safety reasons did not alter our findings (data not shown)(8).

Similar trends for CIN2 were observed in the ASCUS referral population (4.7% in the CM arm and 7.9% in the IC arm), the ASCUS referral population restricted to those who tested hc2 positive (8.2% in the CM arm and 12.8% in the IC arm), and the LSIL referral population (7.6% in the CM arm and 13.8% in the IC arm). The differences in proportion of CIN2 diagnosed in

the CM versus the IC arms were less pronounced in women 30 and older (4.2% in the CM arm and 5.5% in the IC arm) than in women under the age of 30 (6.4% in the CM arm and 11.7% in the IC arm) but this age-specific effect did not reach statistical significance ($p = 0.3$).

Stratifying on the HPV risk group, this trend (of relative increase in number of CIN2 diagnoses by fraction of women sent to colposcopy within a study arm) was also observed among women with enrollment HR HPV infections (excluding HPV16) infections ($p_{\text{trend}} = 0.01$); the trend ($p_{\text{trend}} = 0.1$) was non-significant among women with HPV16, although women in the IC arm had relatively more CIN2 than in the other study arms. A similar pattern was observed for the clinical center histologic diagnoses although the clinical center pathologists tended to call more CIN2 and less $\geq$ CIN3 in general than QC Pathology (Table 4).

The timing of the diagnosis of CIN2 and $\geq$ CIN3 by study arm is shown in Figure 1. Of note, there were significantly fewer cases of both CIN2 and $\geq$ CIN3 diagnosed at enrollment in the CM arm of the trial. There was a significantly fewer two-year cumulative CIN2 histologic diagnoses by study arm (Conservative Management Arm [CM] < HPV Triage Arm [HPV] < Immediate Colposcopy Arm [IC]) relative to two-year cumulative $\geq$ CIN3 at enrollment but not during follow-up ($p_{\text{trend}} = 0.5$) and exit ($p_{\text{trend}} = 0.3$). The CIN2: $\geq$ CIN3 in the CM arm at enrollment was 0.40, a 3-fold lower than the ratio in the IC arm ($p_{\text{trend}} < 0.001$ by study arm), further evidence that the aggressiveness of the study arm in the colposcopy referral at enrollment influenced the overall number of CIN2 diagnosed over the 2 years within a study arm. There were no observed differences in the ratio of CIN2: $\geq$ CIN3 by study arm during follow-up ($p_{\text{trend}} = 0.5$) and exit ($p_{\text{trend}} = 0.3$), i.e., similar increases in cumulative incidence CIN2 and CIN3 and the relatively stable CIN2: $\geq$ CIN3 ratio in each arm, reflecting that women in all arms were managed similarly after enrollment.

CIN2 diagnoses by QC Pathology that were called less than CIN2 or CIN2 by the clinical center pathologists were the most likely to be under-represented in the CM arm compared to the IC arm (Table 3). For example, the ratio of the number of QC pathology diagnosed CIN2 in the CM arm versus the IC arm among those diagnosed as less than CIN2 by clinical center pathologists was 0.40. By comparison, the ratio was 0.74 among diagnosed as CIN3 or more severe by the clinical center pathologists. Overall, there was a marginally significant trend of increasing differences in the number of CIN2 between study arms by less severe diagnosis by the clinical center pathologists ($p_{\text{trend}} = 0.07$). A similar pattern was observed when restricted to only HR HPV (excluding HPV16)-positive CIN2 ($p_{\text{trend}} = 0.07$).

Discussion

We previously have shown that a portion of CIN2 diagnoses are also due to misclassification of disease (3;19) and to HPV infections by non-HR HPV genotypes (3). Here, we present data from ALTS showing that a significant portion of CIN2 diagnosed by central panel review, even caused by HR HPV genotypes, may represent only regressive lesions. Similar patterns were observed in the ASCUS referral population, in the ASCUS referrals that tested hc2 positive, and in the LSIL referral population. We estimated that approximately 40% of rigorously-defined CIN2 diagnoses in primarily young women (mean age = 24.8 years, median age = 23 years, range = 18–62 years) were destined to resolve on their own by using a “subtractive” analytic approach that compared the fraction found in the least sensitive (CM) and most sensitive (IC) study arm (by virtue of the proportion of women in arm referred to colposcopy) for detection of cervical abnormalities. The differences in CIN2 detection are due to the delay in the colposcopic evaluation of patients. Importantly, the time difference in diagnostic evaluation was assigned by the randomization, which created comparable populations. By comparison, 27% (20) and 19% (21) of histologically-confirmed CIN2 regressed over approximately 2 years of follow-up in the placebo arms of two chemoprevention trials.

We used $\geq$ CIN3 as a reference to show that the study arms were roughly equivalent in cancer risk, and the differences in the criteria for enrollment colposcopy primarily affected the fraction of women diagnosed with CIN2. However, we note that, in addition to some CIN2 regressing, some HPV infections may have caused incident CIN2 while some CIN2 may have “progressed” to CIN3. Thus CIN2 regression cannot be precisely determined although reasonable estimations can be derived.

It is also worth mentioning that CIN2 is the least reproducible of all cervical diagnoses (19; 22), and it is possible that the regressive nature of CIN2 will depend somewhat on the individual pathologist diagnosing it. As shown in table 2, this lack of agreement is directly related to the regression of CIN2: the likelihood of regression correlated with the severity of the second (original) diagnosis by the clinical center. For scientific rigor, we used the histopathologic diagnoses rendered by the Pathology Quality Control Group review in our analysis. Yet, we observed a similar difference in the fraction of CIN2 as diagnosed by the clinical center pathologists between the CM and IC arms.

In real-world settings, some clinical pathologists equivocate on the use of a CIN2 diagnosis, relying on non-standard diagnoses such as “CIN1-2” or “CIN2-3”. Their use may reflect further the uncertain nature of CIN2. It is plausible that each diagnosis will represent different likelihoods of regression although it is unclear how reliable such distinctions are, given how generally unreliable a CIN2 diagnosis is (19;22). The inclusion of lesions of an even more ambiguous nature in the definition of CIN2 would be expected to increase the overall regressive potential of CIN2. The use of equivocations like CIN1/2 should probably be discouraged given the lack of evidence of utility, unproven reliability, and the possible increase in the number of women receiving unnecessary therapy.

We point out that the CIN2 diagnosed at enrollment followed an ASCUS or LSIL Pap smear, which led to referral into the study. That is, women were not referred into ALTS because of a HSIL Pap smear. In ALTS, we previously found that women with biopsy-diagnosed CIN2 following the HSIL enrollment cytology (n.b., women enrolled into ALTS had cytology repeated at the enrollment visit) were more apt to have an underlying CIN3 than those with a less severe enrollment cytology (3). We therefore hypothesize that CIN2 following a HSIL cytology may be on average less regressive than that observed for CIN2 diagnosed in the ALTS population.

A CIN2 diagnosis on biopsy is the clinical threshold for treatment in the U.S., its treatment provides a margin of safety against cancer risk. However, a greater recognition of the true equivocal nature of CIN2 is needed. Aggressive clinical management of young women (median age = 25 years; mean age = 27.5 years in ALTS) who have ASCUS or LSIL cytology will lead to over-diagnosis of CIN2 and over-treatment of a significant number of regressive lesions. This is an important clinical issue since most CIN2 is diagnosed in women following ASCUS or LSIL cytology (23).

From these data, we suggest that strategies that send more women to colposcopy, such as immediate colposcopy for LSIL or ASC-US or HPV triage of ASC-US, offer the benefit of early detection of CIN3 at the cost of increased detection of CIN2, some proportion of which is destined to resolve and its treatment translates into patient morbidity without benefit. Repeat cytology at an ASCUS threshold as recommended, rather than a HSIL threshold as used in CM arm of ALTS, would be expected to yield different results, with more women going to colposcopy and higher proportion of CIN2 i.e., more akin to the IC and HPV arms of ALTS. However, this is only speculative since we did not evaluate this clinical algorithm in ALTS.

HPV16-positive CIN2 appears less likely to regress, perhaps as the result of its greater tendency to persist and its greater oncogenic potential to progress to precancerous lesions than other

HPV genotypes (24). When HPV genotyping from validated tests becomes routinely available, detection of HPV16 may be a useful stratifier of risk (25) for deciding the clinical management of CIN2 diagnoses: HPV16-negative CIN2 diagnosed in young women with ASCUS or LSIL cytology could be managed less aggressively through increased surveillance rather than immediate treatment (1;4) while HPV16-positive CIN2, the most strongly linked with CIN3 (3) and least regressive, probably warrants inclusion with CIN3 for management.

More generally, a clinical trial to determine the best management strategies for CIN2, akin to ALTS for ASCUS and LSIL Pap smears, is needed. Several biomarkers, such as HPV genotyping and p16^{INK4A} immunostaining (26–28), warrant evaluation for determining which women with CIN2 need immediate treatment versus surveillance. Key outcomes for any triage strategy for CIN2 would be the timely detection of CIN3 (misclassified as CIN2 (3) or progression of a carcinogenic HPV infection, diagnosed as CIN2, to CIN3), safety against cancer, and the reduction in the number of women with CIN2 treated as compared to the current standard-of-care (4) of excising treatment for all women diagnosed with CIN2.

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Figure 1.

compares of the 2-year cumulative QC pathology-diagnosed cervical intraepithelial neoplasia grade 2 (CIN2) (■) and CIN3 or worse ($\geq$ CIN3) (■) by timing of diagnosis (enrollment, follow-up, and exit), stratified by study arm; “+ Follow-up” and “+ Exit” indicate the number of cases diagnosed in that time period were added to the total number of cases diagnosed in the previous time period. The numeric value above each pair of bars represents the CIN2 to $\geq$ CIN3 ratio. IC, Immediate Colposcopy arm; HPV, HPV arm; CM, Conservative Management arm

Table 1

Demographics and risk factors for women with a worst 2-year diagnosis by the Pathology Quality Control Group of <CIN2, CIN2, or ≥CIN3

	<CIN2	CIN2	≥CIN2	Total
Center				
1	1,242	131	175	1,548
	30.2%	33.1%	32.3%	
2	729	85	98	912
	17.7%	21.5%	18.1%	
3	895	58	92	1,045
	21.8%	14.6%	17.0%	
4	1,248	122	177	1,547
	30.3%	30.8%	32.7%	
Referral Pap				
ASCUS	2,945	232	306	3,483
	71.6%	58.6%	56.5%	
LSIL	1,169	164	236	1,569
	28.4%	41.4%	43.5%	
Smoker				
Never	2,273	194	213	2,680
	55.3%	49.0%	39.3%	
Former	504	43	61	608
	12.3%	10.9%	11.3%	
Current	1,331	158	268	1,757
	32.4%	39.9%	49.4%	
Missing	6	1	0	7
	0.1%	0.3%	0.0%	
Oral Contraceptive User				
Never Used Contraceptives	92	3	8	103
	2.2%	0.8%	1.5%	
Never	1,615	133	191	1,939
	39.3%	33.6%	35.2%	
Former	658	76	95	829
	16.0%	19.2%	17.5%	
Current	1,726	181	247	2,154
	42.0%	45.7%	45.6%	
Missing	23	3	1	27
	0.6%	0.8%	0.2%	
Parity				
Never Pregnant	1,175	120	156	1,451
	28.6%	30.3%	28.8%	
No Births	532	49	67	648
	12.9%	12.4%	12.4%	
1 Birth	1,035	112	136	1,283

	<CIN2	CIN2	≥CIN2	Total
	25.2%	28.3%	25.1%	
2 Births	777	67	124	968
	18.9%	16.9%	22.9%	
3 or More Births	592	48	59	699
	14.4%	12.1%	10.9%	
Missing	3	0	0	3
	0.1%	0.0%	0.0%	
Education				
Grade 1–6	23	2	1	26
	0.6%	0.5%	0.2%	
Grade 7 1–12	578	81	130	789
	14.0%	20.5%	24.0%	
Completed High School/GED	1,275	113	161	1,549
	31.0%	28.5%	29.7%	
Vocational/Trade School	221	22	29	272
	5.4%	5.6%	5.4%	
Some College	1,323	138	168	1,629
Some College	32.2%	34.8%	31.0%	
Completed College	493	32	43	568
	12.0%	8.1%	7.9%	
Some/Completed Graduate School	198	8	10	216
	4.8%	2.0%	1.8%	
Missing	3	0	0	3
	0.1%	0.0%	0.0%	
Race				
White/Hispanic	158	16	12	186
	3.8%	4.0%	2.2%	
White/Non-Hispanic	2,397	238	378	
	58.3%	60.1%	69.7%	
Black	1,315	119	119	1,553
	32.0%	30.1%	22.0%	
Asian or Pacific Islander	140	11	18	169
Asian or Pacific Islander	3.4%	2.8%	3.3%	
American Indian or Alaskan Native	88	10	10	108
	2.1%	2.5%	1.8%	
Missing	16	2	5	23
	0.4%	0.5%	0.9%	
Total	4,114	396	542	5,052

Table 2

A comparison of 2-year cumulative worst histologic diagnosis by QC Pathology by study arm and human papillomavirus (HPV) risk group. There was a significant trend ($p_{\text{trend}} < 0.001$) of fewer two-year cumulative CIN2 histologic diagnoses by study arm (Conservative Management Arm [CM] < HPV Triage Arm [HPV] < Immediate Colposcopy Arm [IC]) relative to two-year cumulative $\geq$ CIN3. CIN, cervical intraepithelial neoplasia; CIN2: $\geq$ CIN3, the ratio of CIN2 to $\geq$ CIN3.

		<CIN2	CIN2	$\geq$ CIN3	Total	CIN2/CIN3
Study Arm = CM						
HPV-	n	494	3	5	502	0.60
	row%	98.4%	0.6%	1.0%		
Non-Carcinogenic	n	214	6	7	227	0.86
	row%	94.3%	2.6%	3.1%		
Carcinogenic	n	666	62	77	805	0.81
	row%	82.7%	7.7%	9.6%		
HPV16	n	157	35	112	304	0.31
	row%	51.6%	11.5%	36.8%		
Total	n	1,531	106	201	1,838	0.53
	row%	83.3%	5.8%	10.9%		
Study Arm = HPV						
HPV-	n	415	1	3	419	0.33
	row%	99.0%	0.2%	0.7%		
Non-Carcinogenic	n	167	13	5	161	2.60
	row%	103.7%	8.1%	3.1%		
Carcinogenic	n	436	66	55	557	1.20
	row%	78.3%	11.8%	9.9%		
HPV16	n	113	28	79	220	0.35
	row%	51.4%	12.7%	35.9%		
Total	n	1,131	108	142	1,381	0.76
	row%	81.9%	7.8%	10.3%		
Study Arm = IC						
HPV-	n	435	8	12	455	0.67
	row%	95.6%	1.8%	2.6%		

		<CIN2	CIN2	≥CIN3	Total	CIN2/CIN3
Non-Carcinogenic	n	204	17	9	230	1.89
	row%	88.7%	7.4%	3.9%		
Carcinogenic	n	655	111	78	844	1.42
	row%	77.6%	13.2%	9.2%		
HPV16	n	158	46	100	304	0.46
	row%	52.0%	15.1%	32.9%		
Total	n	1,452	182	199	1,833	0.91
	row%	79.2%	9.9%	10.9%		

* The reason for the lower number of subjects in the HPV arm is that the HPV arm was closed prematurely for the women referred with a low-grade squamous intraepithelial Pap because of lack of utility for HPV triage in this population.

Table 3

The distribution of 2-year cumulative QC Pathology-diagnosed cervical intraepithelial neoplasia grade 2 (CIN2) by study arm and the worst diagnosis rendered by clinical center (CC) pathologists. Panel A shows the distribution of all CIN2 and panel B for only those women who tested positive for HR HPV (excluding HPV16) at baseline. There was a marginally significant trend of a greater difference in the number of any QC Pathology-diagnosed CIN2 ($p_{\text{trend}} = 0.07$) and HR HPV (excluding HPV16)-positive CIN2 ($p_{\text{trend}} = 0.07$) between study arms with fewer versus more referrals to colposcopy at baseline (Conservative Management Arm [CM] < HPV Triage Arm [HPV] < Immediate Colposcopy Arm [IC]) with less severe diagnoses by the clinical center pathologists. CM:IC represents the ratio of diagnoses in the CM study arm versus the IC study arm.

A. All CIN2				
CC Diagnosis				
Study Arm	<CIN2	CIN2	CIN3	Total
CM	23	63	20	106
HPV*	31	57	21	109
IC	58	97	27	182
Total	112	217	68	397
CM:IC	0.40	0.65	0.74	0.58

B. Carcinogenic HPV-positive (excluding HPV16) CIN2				
CC Diagnosis				
Study Arm	<CIN2	CIN2	CIN3	Total
CM	13	35	14	62
HPV*	27	28	11	66
IC	38	59	14	111
Total	78	122	39	239
CM:IC	0.34	0.59	1.00	0.56

* The reason for the lower number of subjects with CIN2 in the HPV arm is that the HPV arm was closed prematurely for the women referred with a low-grade squamous intraepithelial Pap because of lack of utility for HPV triage in this population.

Table 4

A comparison of worst 2-year histologic diagnosis by the clinical center pathologists by study arm and HPV risk group. CIN, cervical intraepithelial neoplasia; CIN2:≥CIN3, the ratio of CIN2 to ≥CIN3, IC, Immediate Colposcopy arm; HPV, HPV arm; CM, Conservative Management arm

		<CIN2	CIN2	≥CIN3	Total	CIN2/CIN3
Study Arm = CM						
HPV-	n	491	11	0	502	n/a
	row%	97.8%	2.2%	0.0%		
Non-Carcinogenic	n	210	10	7	227	1.4
	row%	92.5%	4.4%	3.1%		
Carcinogenic	n	661	82	62	831	1.3
	row%	79.5%	9.9%	7.5%		
HPV16	n	157	53	94	304	0.6
	row%	51.6%	17.4%	30.9%		
Total	n	1,519	156	163	1,838	1.0
	row%	82.6%	8.5%	8.9%		
Study Arm = HPV						
HPV-	n	414	4	1	419	4.0
	row%	98.8%	1.0%	0.2%		
Non-Carcinogenic	n	167	16	2	185	8.0
	row%	90.3%	8.6%	1.1%		
Carcinogenic	n	448	66	43	557	1.5
	row%	80.4%	11.8%	7.7%		
HPV16	n	115	50	55	220	0.9
	row%	52.3%	22.7%	25.0%		
Total	n	1,144	136	101	1,381	1.3
	row%	82.8%	9.9%	7.3%		
Study Arm = IC						
HPV-	n	433	17	5	455	3.4
	row%	95.2%	3.7%	1.1%		
Non-Carcinogenic	n	203	21	6	230	3.5

		<CIN2	CIN2	≥CIN3	Total	CIN2/CIN3
Carcinogenic	row%	88.3%	9.1%	2.6%		
	n	661	122	61	844	2.0
HPV16	row%	78.3%	14.5%	7.2%		
	n	161	61	82	304	0.7
Total	row%	53.0%	20.1%	27.0%		
	n	1,458	221	154	1,833	1.4
	row%	79.5%	12.1%	8.4%		

* The reason for the lower number of subjects in the HPV arm is that the HPV arm was closed prematurely for the women referred with a low-grade squamous intraepithelial Pap because of lack of utility for HPV triage in this population.