Prospective follow-up suggests similar risk of subsequent cervical intraepithelial neoplasia grade 2 or 3 among women with cervical intraepithelial neoplasia grade 1 or negative colposcopy and directed biopsy

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OBJECTIVE: The purpose of this study was to determine the risk of cumulative cervical intraepithelial neoplasia (CIN) grade 2 or 3 according to initial colposcopy and directed biopsy results among women with low-grade squamous intraepithelial lesions (LSIL) or human papillomavirus (HPV) DNA positive atypical squamous cells of undetermined significance (ASCUS).

STUDY DESIGN: A 2-year follow-up of 897 cases of LSIL and 1193 cases of HPV DNA positive ASCUS from the ASCUS/LSIL Triage Study was used to simulate American Society for Colposcopy and Cervical Pathology Consensus Conference recommendations. Women with CIN grade 1 or less were followed up for 2 years by semiannual cytologic examination, with universal exit colposcopy. The clinical end point was a cumulative clinical center histologic diagnosis of CIN grade 2 or 3.

RESULTS: The cumulative risk of CIN grade 2 or 3 was equivalent for LSIL (27.6%) and HPV positive ASCUS (26.7%). After excluding the women with a diagnosis of CIN grade 2 or 3 at initial colposcopy and directed biopsy (17.9%), the remaining women were at nearly identical risk for subsequent CIN grade 2 or 3 regardless of initial colposcopy result (completely negative colposcopy—11.3%; negative colposcopically directed biopsy—11.7%; and CIN grade 1 biopsy—13.0%).

CONCLUSION: LSIL and HPV positive ASCUS are clinically equivalent. Initial colposcopic detection of obviously prevalent CIN grade 2 or 3 reduces risk. However, for the remaining women who have CIN grade 1 or less on colposcopy and directed biopsy, the risk for subsequent CIN grade 2 or 3 (whether missed, prevalent, or truly incident) is approximately 12% over 2 years. This risk does not vary meaningfully by initial distinction of histologic CIN grade 1 from negative colposcopy and biopsy. (Am J Obstet Gynecol 2003;188:1406-12.)

Key words: Atypical squamous cells of undetermined significance, low-grade squamous intraepithelial lesions, cervical intraepithelial neoplasia, human papillomavirus, clinical treatment, colposcopy

Widespread dissemination of the American Society for Colposcopy and Cervical Pathology (ASCCP) "Consensus Guidelines" will alter the patterns of treatment of mild cervical cytologic and histologic abnormalities in the United States.[1,2] The new guidelines are based on empiric evidence regarding the natural history of human papillomavirus (HPV) infection, and make use of the most recent clinical trial data on optimal management of atypical squamous cells of undetermined significance (ASCUS) and low-grade squamous intraepithelial lesions (LSIL).[3-6] However, the impact of new guidelines on the numbers of colposcopic referrals, the types of patients referred, and their proper clinical management after colposcopy have not been studied formally, which was the motivation for this article and the following article.[7]

A striking change from current colposcopic referral patterns will occur if two options in the guidelines both become standard practice, namely, HPV DNA triage of ASCUS and immediate colposcopic referral of LSIL.[1,5,6] If so, approximately one half of the women with cytologic ASCUS (those with positive test results for oncogenic or

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**A complete list of ALTS investigators begins on page 1411.*

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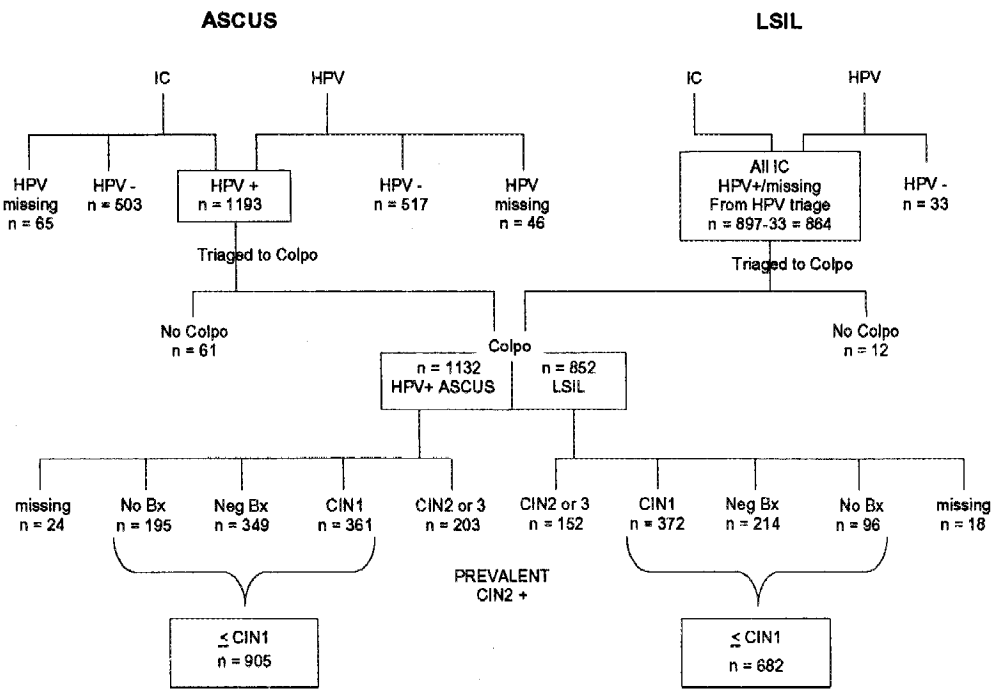

Figure Description of study population derived from women with LSIL or HPV positive ASCUS in the IC and HPV triage study arms of ALTS. *Colpo,* Colposcopy; *Bx,* biopsy; *Neg,* negative.

"high-risk" types of HPV DNA[>1 million women in the United States annually]) will be referred to colposcopy along with an additional 1 million women with LSIL.

Women found to have histologic cervical intraepithelial neoplasia (CIN) grade 2 or more on colposcopically directed biopsy will be treated by either ablative or excisional procedures,[2] but the optimal postcolposcopy management of the remaining majority of women who are found to have only CIN grade 1 or less has not been defined. It would be valuable to distinguish subgroups at higher or lower risk for the development of cervical cancer to more safely and efficiently determine management. At present there is no validated, more specific marker for risk than the identification of oncogenic HPV types, but approximately 83%[3] of the 1 million women with LSIL and all of the 1 million women with ASCUS[4] that were evaluated by colposcopy under the new ASCCP guidelines would be high-risk HPV positive.

Clinicians have traditionally relied on colposcopically directed biopsy results to guide management after colposcopy. When the primary differential in management was between disease that was detected and disease that was not found, all women with any level of CIN were treated, and only women who had negative results at colposcopy were followed. However, the trend towards expectant management of women with CIN grade 1,[2,8,9] reserving treatment for CIN grade 2 and 3,[2] has increased the importance of histologic differentiation of CIN grade 1 from CIN grade 2 or 3. In addition, the risk that is associated with "histologically confirmed" CIN grade 1 has been considered to be higher than that associated with negative colposcopic and histologic findings, and the management often has varied accordingly, but without a firm empiric basis.[10] In fact, significant underdiagnosis of CIN grade 2 or 3 that has been noted in a number of studies of women with low-grade Papanicolaou test abnormalities,[11-14] along with only moderate interobserver agreement in pathologic evaluation,[15] has raised the issue of the reliability of initial diagnosis of ≤CIN grade 1.

To examine optimal management after colposcopy among the population of women who are likely to be referred to colposcopy under the new ASCCP guidelines, we analyzed data from the ASCUS-LSIL Triage Study (ALTS). The analysis is divided into two parts. In this article, we will show that, surprisingly, the ALTS data did not demonstrate a difference in the risk of subsequent CIN grade 2 or 3 between women with histologic CIN grade 1 and women with no CIN at initial colposcopy. Therefore, once initial colposcopy and directed biopsy excluded obviously prevalent CIN grade 2 or 3, the remaining women should be managed similarly. In the following article,[7] postcolposcopic management options for the combined patient population of women with ≤CIN grade 1 are addressed.

Methods

A more detailed description of ALTS may be found in the first of the accompanying articles[6] and is published

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Table I. HPV test result by referral cytologic interpretation, for IC and HPV triage study arms combined

HPV test result	*ASCUS (No. [%])*	*LSIL (No. [%])*
Missing	111 (4.8%)*	46 (5.1%)
Negative	1020 (43.9%)	130 (14.5%)†
Positive	1193 (51.3%)	721 (80.4%)
Total	2324 (100.0%)	897 (100.0%)

*For this analysis, missing HPV results for ASCUS (4.8%) were excluded.

†Excluded from this analysis were 33 women with LSIL who were assigned randomly to the truncated HPV triage study arm and not referred to colposcopy.

Table III. Clinical center first colposcopy and directed biopsy results by referral group

Colposcopy and directed biopsy result	*HPV+ ASCUS (No. [%])*	*LSIL (No. [%])*
Missing biopsy	24 (2.1%)	18 (2.1%)
Normal colposcopy, no biopsy	195 (17.2%)	96 (11.3%)
Negative biopsy	349 (30.8%)	214 (25.1%)
CIN grade 1	361 (31.9%)	372 (43.7%)
CIN grade 2 or 3	203 (17.9%)	152 (17.8%)
Total	1132 (100.0%)	852 (100.0%)

Excludes 106 women who did not attend initial colposcopy visit, 61 women with HPV+ ASCUS and 45 women with LSIL. $P_{trend} < .001$ by χ^2 test for association of histopathologic diagnosis and referral group (excluding missing values).

fully elsewhere.[16] Only a few specific methodologic points will be made here.

ALTS included three randomization arms, but the conservative management arm relied on a program of repeated cytologic tests that did not refer a high percentage of women with CIN grade 2 or 3 to colposcopy at enrollment.[4] In contrast, the HPV triage arm was as sensitive as the immediate colposcopy (IC) arm in the detection of CIN grade 2 or 3 at enrollment. To simulate a triage strategy of referring women with ASCUS cytology who are HPV positive (HPV+ ASCUS) and all women with LSIL cytology to colposcopy, we restricted this analysis to the IC and HPV triage arms (Figure).

We used the original cytologic diagnoses from the referring community laboratories (ASCUS or LSIL) rather than the review diagnosis by an expert pathology quality control (QC) group, to reflect normal practice more closely. Of note, ALTS was conducted before the 2001 Bethesda System[17] that redefined ASCUS, by eliminating "ASCUS favor reactive" and adding "ASC cannot rule out HSIL (high-grade squamous intraepithelial lesion)." Unless the modifications result in a much more restricted ASCUS than anticipated, the findings that are based on the previous terminology still will be fully applicable. For the ASCUS population, the enrollment Hybrid Capture 2 result was used to identify HPV+ ASCUS.

Table II. Cumulative diagnoses* of two disease end points, by referral group

	HPV+ ASCUS (n = 1193) Percentage (CI)	*LSIL (n = 897) Percentage (CI)*
Clinical center CIN grade 2 or 3	26.7 (24.2-29.3)	27.6 (24.7-30.7)
Pathology QC group CIN grade 3	14.5 (12.6-16.6)	15.9 (13.6-18.5)

*Percentage of women diagnosed with the disease end points at any time during ALTS: enrollment, 2-year follow-up, or exit.

Of the 1193 women with HPV+ ASCUS, 61 women did not return for scheduled enrollment colposcopy. Of the 897 women with LSIL, 45 women did not have enrollment colposcopy. Thirty-three of these 45 women were HPV negative in the HPV triage arm and were not referred to colposcopy on the basis of the ALTS protocol[5]; the remaining 12 women did not return for scheduled colposcopy. The study population therefore included 1132 women with HPV+ ASCUS and 852 women with LSIL (N = 1984) from the IC and HPV arms who underwent enrollment colposcopy (Figure).

This population underwent routine follow-up examinations at 6, 12, and 18 months. At the follow-up visits, participants had a pelvic examination that was similar to that at enrollment, a cervical cell collection for the preparation of a ThinPrep cytology (Cytyc, Boxborough, Mass), masked HPV testing (Hybrid Capture 2; Digene Corporation, Gaithersburg, Md), and two replicate masked Cervigrams (National Testing Laboratories Worldwide, Fenton, Mo). A cytology result of HSIL triggered rereferral to colposcopy during follow-up examinations. All participants in the trial underwent an exit visit at the 24-month time period that included colposcopy. At this visit alone, all the available clinical center and pathology QC group cytology and histology, HPV results from the previous visits, and the last cervigram (in the form of a photograph) were available to the clinician who performed the colposcopy. Details of patient treatment and test procedures are found elsewhere.[6,16]

A pathology QC group reviewed the cytologic and histologic specimens for purposes of disease definition and to provide a safety net for study participants.[6] However, unless there was a safety net trigger, clinical treatment was based on the reading by the clinical center pathologist. The QC of HPV testing and colposcopy in ALTS is detailed elsewhere.[6,16]

For the clinical endpoint, we used the cumulative histologic diagnosis of CIN grade 2 or 3 by pathologists at the four ALTS clinical centers over the 2-year follow-up. We supplemented this main analysis using our best surrogate for cancer risk, namely, the histologic end point of CIN grade 3 as diagnosed by the pathology QC group. The statistical analysis relied on standard contingency table methods to compare the cumulative risk of CIN

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Table IV. Risk of subsequent CIN grade 2 or 3 diagnoses by the clinical centers and CIN grade 3 diagnosis by pathology QC group, according to first colposcopy and directed biopsy result*

Cumulative risk	*HPV+ ASCUS (n/N)*	*LSIL (n/N)*	*All (n/N)*
Subsequent CIN grade 2 or 3 diagnosis: colpobiopsy result (clinical centers)			
Normal colposcopy, no biopsy result	25/195 (12.8%)	8/96 (8.3%)	33/291 (11.3%)
Negative biopsy result	37/349 (10.6%)	29/214 (13.6%)	66/563 (11.7%)
CIN grade 1	45/361 (12.5%)	50/372 (13.4%)	95/733 (13.0%)
P_{trend} (column)	.99	.26	.43
Subsequent CIN grade 3 diagnosis: colpobiopsy result (pathology QC group)			
Normal colposcopy, no biopsy result	13/195 (6.7%)	5/96 (5.2%)	18/291 (6.2%)
Negative biopsy result	24/349 (6.9%)	13/214 (6.1%)	37/563 (6.6%)
CIN grade 1	26/361 (7.2%)	39/372 (10.5%)	65/733 (8.9%)
P_{trend} (column)	.81	.04†	.10‡

*Women with CIN grade 2 or 3 at first colposcopy were excluded.
†χ^2 test, 0.09.
‡χ^2 test, 0.19.

grade 2 and 3 end points among different groups of women in the trial.

Results

In the IC and HPV triage arms, there were 2324 cases of ASCUS, of which 1193 cases (51.3%) were HPV DNA positive, which led to inclusion in the study group (Table I). Of the 897 LSIL women in these two arms, 721 (80.4%) had HPV-positive results, but all the women were included because all the women would be referred under the new guidelines without testing for HPV DNA.

In Table II, the overall cumulative risk of CIN grade 2 or 3 at enrollment, during follow-up, and at exit is shown for HPV+ ASCUS and for LSIL separately, to justify combining these groups after colposcopy. Of the 1193 women with HPV+ ASCUS, cumulative CIN grade 2 or 3 totaled 26.7% (CI, 24.2%-29.3%); of the 897 women with LSIL, the cumulative CIN grade 2 or 3 was nearly identical at 27.6% (CI, 24.7%-30.7%). Cumulative diagnoses of CIN grade 3 by the pathology QC group were also similar, with CIN grade 3 detected in 14.5% of the women (range, 12.6%-16.6%) with HPV+ ASCUS and in 15.9% of the women (range, 13.6%-18.5%) with LSIL.

The results of the enrollment colposcopically directed biopsy specimens of HPV+ ASCUS and LSIL are shown in Table III. This table and the following tables are restricted to women who attended colposcopy. Of the 1132 women with HPV+ ASCUS who attended colposcopy, 195 women (17.2%) were felt to be colposcopically normal and did not undergo biopsy, whereas 349 women (30.8%) did undergo biopsy but were histology negative. Only 96 women (11.3%) of the 852 women with LSIL did not undergo biopsy because of a normal colposcopic impression, but the rate of negative biopsy results (25.1%) was similar to HPV+ ASCUS referral. Detection of CIN grade 1 was more common among women with LSIL (43.7%) than for women with HPV+ ASCUS (31.9%). This difference was statistically significant, which indicated that cytologic LSIL was associated more highly with histologic CIN grade 1 than was HPV+ ASCUS. But, more important, the risk of finding histologic CIN grade 2 or 3 did not differ between women with HPV+ ASCUS and women with LSIL: 203 women (17.9%) with HPV+ ASCUS and 152 women (17.8%) with LSIL had CIN grade 2 or 3 at initial colposcopy and directed biopsy.

Table IV shows the risk of CIN grade 2 or 3 that was diagnosed subsequently by the clinical center pathologists during follow-up, among women with ≤CIN grade 1 at initial colposcopy and directed biopsy. Among all of these women, the subset with HPV+ ASCUS or those women with LSIL, the risk of CIN grade 2 or 3 did not vary significantly by the initial colposcopy and biopsy result. Similarly, Table IV also details the risk of subsequent pathology QC–interpreted CIN grade 3 according to first colposcopically directed biopsy result. Women with ≤CIN grade 1 at initial colposcopic evaluation were at similar risk for subsequent detection of CIN grade 3, whether they had LSIL or HPV+ ASCUS. As a small exception of limited clinical importance, only among women with LSIL, there was a marginal tendency for a higher risk of subsequent CIN grade 3 that was associated with CIN grade 1 compared with <CIN grade 1.

Comment

The ASCCP Consensus Guidelines recommend colposcopy for all women with LSIL and HPV+ ASCUS.[1] The rate of HPV positivity with ASCUS varies depending on patient population characteristics such as age and sexual risk factors[18] and on the criteria applied by the laboratory in making the interpretation of ASCUS.[19] Nonetheless, the overall ALTS rate of 51.3% (Table I) that was derived from multiple laboratories and from a diverse population of women, approximates the percentage of women with ASCUS in the United States who are likely to be referred to colposcopy. This would result in 1 to 1.5 million women with ASCUS and 1 to 1.25 million more women with LSIL, or a total of 2 to 2.75 million women who will be referred annually for colposcopic evaluation.

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We found that the 2-year cumulative risk of CIN grade 2 or 3, which was diagnosed by the clinical center pathologists, was virtually the same for women with LSIL and HPV+ ASCUS (27.6% and 26.7%, respectively). The risk of CIN grade 3 that was diagnosed by the pathology QC group, which was the more stringent surrogate for cancer risk, was also similar for both groups. But we considered the endpoint of CIN grade 2 or 3 that was diagnosed at the clinical center to be more relevant for clinicians because this is the threshold for treatment per current practice.

We observed that women who were referred for the evaluation of HPV+ ASCUS were somewhat more likely than the women who were referred for LSIL to either have a negative colposcopy or to undergo biopsy but to have negative histology. Therefore, the risk of any CIN being documented at initial colposcopy was approximately 12% less for women who were referred for HPV+ ASCUS than for women who were referred for LSIL (overall risk for any CIN was 50% for HPV+ ASCUS vs 62% for LSIL). This difference in initial risk was entirely due to the 12% increase in histologic CIN grade 1 after an LSIL interpretation compared with HPV+ ASCUS. In contrast, both LSIL and HPV+ ASCUS had an 18% risk of CIN grade 2 or 3 that was detected at initial colposcopically directed biopsy, which clearly indicated the need for identical initial colposcopic management.

Despite less than perfect sensitivity, initial colposcopy and biopsy identifies obviously prevalent CIN grade 2 or 3 (18%) and thereby lowers the risk for the group of remaining women with ≤CIN grade 1 at initial colposcopy. As a result, the cytology interpretations of LSIL and HPV+ ASCUS (before colposcopy) convey a higher risk of cumulative diagnosis of CIN grade 2 or 3 over 2 years (27%) than the risk of subsequent CIN grade 2 or 3 (13%) that is associated with the colposcopic finding of histologic CIN grade 1. We address options for continued follow-up in the accompanying article.[7]

Expectant management of women with documented CIN grade 1 has most commonly included intermittent colposcopy and repeat cytology evaluation, whereas women with negative findings at colposcopy and biopsy have often been followed by cytology only. This difference has been based on the unproven assumption that women who are found to have CIN grade 1 at initial colposcopy are at higher risk for the subsequent detection of CIN grade 2 or 3 than women who were not found to have CIN grade 1. However, the 2-year follow-up in ALTS of women with ≤CIN grade 1 indicates that the risk of the subsequent detection of CIN grade 2 or 3 varies little with respect to the findings at initial colposcopy. Specifically, as suggested in at least one previous publication,[10] there was no meaningful difference in the subsequent risk for CIN grade 2 or 3 between women with no disease documented at initial colposcopy and women with CIN grade 1. The use of the pathology QC diagnosis of CIN grade 3, which we considered the surrogate for cancer risk, did not alter the conclusions.

There are at least two reasons why women who are referred for equivocal and low-grade cytologic interpretations and are not found to have high-grade disease at initial colposcopy remain at risk for the subsequent detection of CIN grade 2 or 3: (1) interobserver variability in colposcopic and histologic interpretations may result in the underdiagnosis of prevalent CIN grade 2 or 3 at initial colposcopy (missed prevalent disease)[11-15]; and (2) the interim development of CIN grade 2 or 3 (incident disease).[20-22] Observer variability and subjectivity of the colposcopic examination influence the sensitivity of detection of CIN grade 2 or 3.[11] Significant interobserver variability has also been noted in the interpretation of histologic CIN, particularly CIN grade 1,[15] that may result in the overtreatment of some women with no disease and the undertreatment of other women with high-grade CIN that was either missed on colposcopic biopsy[13] or misclassified by undergrading of the histologic evidence.[15] These findings raise the issue of the reliability of the initial diagnosis of CIN grade 1 and reinforce the need for some kind of follow-up, regardless of the outcome of initial colposcopy.

In addition to the subjectivity of colposcopy, lesion size may significantly influence colposcopic accuracy. CIN grade 2 or 3 that is detected after ASCUS cytology have been shown to be smaller than those detected after HSIL referral.[23] In fact, many CIN grade 3 lesions that were detected eventually in the ALTS follow-up were small lesions.[24] In some cases, the time interval to detection might have allowed for the lesion to progress to a size that was colposcopically identifiable or for de novo incident CIN grade 2 or 3 to develop within an area of ≤CIN grade 1. These points of natural history do not influence the clinical conclusions of the analysis.

In summary, the proper management of mild cervical abnormalities is highly dependent on the proper definition of the women who are at risk. Initial colposcopy and biopsy after LSIL and HPV+ ASCUS identifies most women who are at risk for CIN grade 2 or 3. However, most women (82%) with these Papanicolaou test abnormalities are found to have ≤CIN grade 1 at initial colposcopy. These women continue to be at risk for the detection of CIN grade 2 or 3 during long-term follow-up and require diligent management. Risk does not vary with respect to the distinction of LSIL from HPV+ ASCUS nor with respect to findings at initial colposcopy once the obviously prevalent cases of CIN grade 2 or 3 have been excluded. Subsequent management, which will be addressed in the companion paper,[7] should therefore be the same.

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The following investigators of the ALTS study have submitted the subsequent disclosure statements:

Richard Guido had done clinical research and consulting for CYTYC and clinical research for Digene.

Kathleen McIntyre-Seltman has received an honorarium for speaking on behalf of CYTYC Corporation.

Nancy Kiviat received supplies for CYTYC to conduct a Senegal-based study.

Thomas Cox is on the Speakers' Bureau and is an occasional consultant for CYTYC, 3M Pharmaceuticals, and Digene.

Mark Sherman's department at Johns Hopkins received research support from Digene.

Attila Lorincz is the Senior Vice President of Research and Development and Chief Scientific Officer of Digene Corporation. He owns stock and retains stock options in the company.

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