# Variance in the Interpretation of Cervical Biopsy Specimens Obtained for Atypical Squamous Cells of Undetermined Significance

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## Abstract

*We sought to determine whether the variability in dysplasia rates in cases of atypical squamous cells of undetermined significance (ASCUS) reflects variability in interpretation of cervical biopsy specimens. In phase 1, 124 biopsy specimens obtained because of a cytologic diagnosis of ASCUS were reviewed independently by 5 experienced pathologists. Diagnostic choices were normal, squamous metaplasia, reactive, indeterminate, low-grade squamous intraepithelial lesion (LSIL), and high-grade squamous intraepithelial lesion (HSIL). The rate of dysplasia ranged from 23% to 51%. All pathologists agreed in 28% of cases. In 52% of cases, the diagnoses ranged from benign to dysplasia. The overall interobserver agreement was poor. In phase 2, 60 cervical biopsy specimens (21 obtained for ASCUS, 22 for LSIL, and 17 for HSIL) were evaluated using the same diagnostic choices. Agreement was better in biopsies performed for HSIL and LSIL compared to those for ASCUS. Intraobserver reproducibility in the interpretation of biopsies performed for ASCUS ranged from poor to excellent. We conclude that variability in the interpretation of biopsy specimens plays an important role in the differences in rates of dysplasia reported for the follow-up of ASCUS.*

The diagnosis of atypical squamous cells of undetermined significance (ASCUS) is defined by the Bethesda System as cellular abnormalities that are more marked than those attributable to reactive changes but that quantitatively or qualitatively fall short of a definitive diagnosis of squamous intraepithelial lesion (SIL).[1] In the United States, approximately 4.4% of cervicovaginal smears are diagnosed as ASCUS.[2] The clinical follow-up of ASCUS is variable, but recommendations are for repeated cytologic evaluation or colposcopy with cervical biopsy, especially when ASCUS is persistent.[3] Thus, a surgical pathology practice encounters a large number of cervical biopsy specimens obtained for ASCUS. In our laboratory, almost half (47%) of the cervical biopsy specimens we evaluate are obtained for further evaluation of ASCUS. The reported dysplasia rate in biopsy specimens obtained as follow-up for a cytologic diagnosis of ASCUS varies widely, from 15% to more than 60%.[4-8] High interobserver and intraobserver variability in the cytologic diagnosis of ASCUS is well known,[9,10] and it is generally assumed that variability in the cytologic diagnosis of ASCUS is responsible for the wide range of frequency of dysplasia reported in the follow-up of ASCUS.[2,11-13] Cervical biopsy is assumed to be the "gold standard" to evaluate the accuracy of a cytologic diagnosis, yet previous studies, looking at cervical biopsies in general, have shown modest to poor interobserver agreement in cervical biopsy interpretation.[14,15]

With this background, we sought to answer the following questions: (1) What is the interobserver variance in the interpretation of biopsy specimens obtained for ASCUS? (2) Is the interobserver variance different in biopsy specimens obtained for ASCUS compared with specimens obtained for a cytologic diagnosis of low-grade SIL (LSIL) or high-grade SIL (HSIL)? (3) What is the intraobserver variance in biopsy

specimens obtained for ASCUS? (4) Does variability in biopsy interpretation have a role in the wide range of rates of dysplasia reported for biopsy specimens obtained for ASCUS?

## Materials and Methods

We retrieved 124 cervical biopsy specimens obtained for follow-up for a Papanicolaou (Pap) smear diagnosis of ASCUS from the surgical pathology files of the M.S. Hershey Medical Center (Hershey, PA) files for a 3-year period (May 1994 to June 1997). No attempt was made to distinguish a first ASCUS diagnosis from multiple diagnoses of ASCUS or to distinguish subtypes of ASCUS (ie, favor reactive or SIL). Of the 124 biopsies, 118 were forceps biopsies, and 6 were cone biopsies or loop electrosurgical excision procedures. A single slide (usually the second of 3 levels) was selected for review based on the slide quality. The slides were circulated in groups of 20 for a period of a few months among a panel of 5 pathologists.

Each of the pathologist reviewers was certified by the American Board of Pathology in Anatomic Pathology, and each had at least 5 years' experience signing out cervical biopsies in tertiary care medical centers. Four of the 5 also had the Added Qualification in Cytopathology from the American Board of Pathology. All had worked together for at least 5 years. One of the pathologists is a recognized expert in gynecologic pathology. Another is fellowship trained in gynecologic pathology, and 2 are fellowship trained in cytopathology. Reviewers were provided with a menu of 6 diagnoses as follows: (1) no pathologic diagnosis, (2) squamous metaplasia, (3) reactive changes, (4) indeterminate (benign vs dysplasia), (5) LSIL (koilocytosis and mild dysplasia), or (6) HSIL (moderate and severe dysplasia and carcinoma in situ). The reviewers were blinded to the original diagnosis but were aware that the biopsies had been performed for ASCUS. They were instructed to approach the diagnosis of the biopsies as they would in routine sign out and to work independently. There was no attempt to define the various diagnostic terms. In the case of more than one diagnosis, the "most severe" diagnosis (ie, highest number) was to be assigned.

After collecting data on the 124 cases, the second phase of the study was initiated to determine intraobserver variance and to compare variance in interpretation of biopsy specimens obtained for ASCUS with those obtained for LSIL and HSIL. Sixty biopsy specimens were selected: 21 obtained for a Pap smear diagnosis of ASCUS, 22 for LSIL, and 17 for HSIL. Of the 21 biopsy specimens obtained for ASCUS, 19 were selected randomly from the original set of 124 to determine intraobserver reproducibility. The slides were placed in chronologic order and distributed in groups of 20 to the same 5 pathologists for their interpretation without knowledge of the previous cytologic or histologic diagnosis. The interval between the collection of the 2 data sets was about 6 months.

Interobserver variance was calculated using the intraclass correlation coefficient (ICC) to determine agreement beyond chance[16] **Table 1**. While closely related to the kappa statistic and having identical numeric parameters, the ICC[16] has the advantage of analyzing data with multiple response levels when observer agreement varies across the possible responses. For measurement of intraobserver variance, we used the weighted kappa statistic.[17] Consensus was defined as agreement by at least 3 pathologists. For statistical purposes, the first 3 diagnoses on the menu (no pathologic diagnosis, squamous metaplasia, and reactive changes) were collapsed into a single benign category because distinction among the 3 benign diagnoses lacks clinical significance.

## Results

### Phase 1

The 124 biopsy specimens yielded 620 diagnoses (124 cases × 5 pathologists) as follows: 81 (13.1%) normal; 84 (13.5%) squamous metaplasia; 189 (30.5%) reactive; 38 (6.1%) indeterminate; 174 (28.1%) LSIL; and 54 (8.7%) HSIL.

A consensus diagnosis was achieved for 114 (91.9%) of the 124 cases as follows: 68% benign, 0% indeterminate, 24% LSIL, and 8% HSIL **Table 2**. For 10 cases, there was no consensus diagnosis. All 5 pathologists agreed on the diagnosis in 35 cases, 4 agreed in an additional 45 cases, and 3 agreed in an additional 34 cases **Table 3**. In 52% of cases,

**Table 1**
**Interpretation of the Intraclass Correlation Coefficient (ICC)**

| ICC Value | Interpretation |
|---|---|
| ≥0.75 | Excellent agreement beyond chance |
| 0.40-0.74 | Fair to good agreement beyond chance |
| <0.40 | Poor agreement beyond chance |

**Table 2**
**Consensus Diagnosis for 114 Cases**

| Diagnosis | Percentage* |
|---|---|
| Benign | 68.4 |
| Indeterminate | 0.0 |
| Low-grade squamous intraepithelial lesion | 23.7 |
| High-grade squamous intraepithelial lesion | 7.9 |
| **Total** | **100.0** |

* For 10 additional cases, there was no consensus.

**Table 3**
**Agreement: Interpretation of Biopsy Specimens Obtained for Atypical Squamous Cells of Undetermined Significance**

| Agreement | No. (%) |
|---|---|
| 5/5 | 35 (28.2) |
| 4/5 | 45 (36.3) |
| 3/5 | 34 (27.4) |
| 1-2/5 | 10 (8.1) |
| **Total** | **124 (100.0)** |

the diagnoses ranged among the 5 pathologists from benign to dysplasia (LSIL or HSIL). In 10 cases (8.1%), the diagnoses ranged from benign to HSIL.

The ICC showed that agreement beyond chance was good for the diagnosis of HSIL (ICC, 0.52), fair for benign diagnoses (ICC, 0.40), and poor for LSIL (ICC, 0.30). The overall interobserver agreement was poor (ICC, 0.34) **Table 4**.

The data from each of the 5 pathologists were analyzed for diagnostic trends. The rates of dysplasia indicated by the 5 pathologists ranged from 23% to 51% **Table 5**. **Table 6** provides details of each pathologist's interpretations compared with the consensus diagnosis. The percentage of cases discrepant with the consensus diagnosis for each pathologist varied between 8.8% and 20.2%. For example, interpretations by pathologist 1 were discrepant "below" (ie, more benign than) the consensus diagnosis in 8 cases and above the consensus in 2 cases. Interpretations of 3 of the other pathologists were more often discrepant above the consensus **Figure 1**. The percentage of indeterminate diagnoses ranged from 0.0% to 14%.

## Phase 2

The results from phase 2 are given in **Table 7**, **Table 8**, and **Table 9**. The consensus diagnoses for 21 biopsy specimens obtained for ASCUS were as follows: 4, no consensus diagnosis; 11, benign diagnoses; 4, LSIL; and 2,

**Table 4**
**Interobserver Agreement: Interpretation of Biopsy Specimens Obtained for Atypical Squamous Cells of Undetermined Significance**

| | Reliability (Confidence Interval) | Interpretation |
|---|---|---|
| Benign | 0.40 (0.31 to 0.49) | Fair |
| Indeterminate | –0.01 (–0.05 to 0.04) | Very poor |
| Low-grade squamous intraepithelial lesion | 0.30 (0.20 to 0.40) | Poor |
| High-grade squamous intraepithelial lesion | 0.52 (0.35 to 0.70) | Good |
| Overall | 0.34 | Poor |

**Table 5**
**Diagnosis by Pathologist for 124 Biopsy Specimens***

| | Pathologist | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 |
| Benign† | 72 | 49 | 57 | 45 | 62 |
| Indeterminate | 6 | 0 | 4 | 14 | 7 |
| Low-grade squamous intraepithelial lesion | 13 | 41 | 30 | 33 | 23 |
| High-grade squamous intraepithelial lesion | 10 | 10 | 9 | 8 | 7 |
| Dysplasia rate | 23 | 51 | 39 | 41 | 31 |

* Data are given as percentages.
† Includes normal, reactive, and squamous metaplasia.

**Table 6**
**Pathologist Interpretation Compared With Consensus Diagnosis in 114 Cases**

| | Pathologist | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 |
| No. (%) of discrepant cases | 10 (8.8) | 23 (20.2) | 15 (13.2) | 21 (18.4) | 16 (14.0) |
| Above consensus | 2 | 20 | 11 | 19 | 9 |
| Below consensus | 8 | 3 | 4 | 2 | 7 |

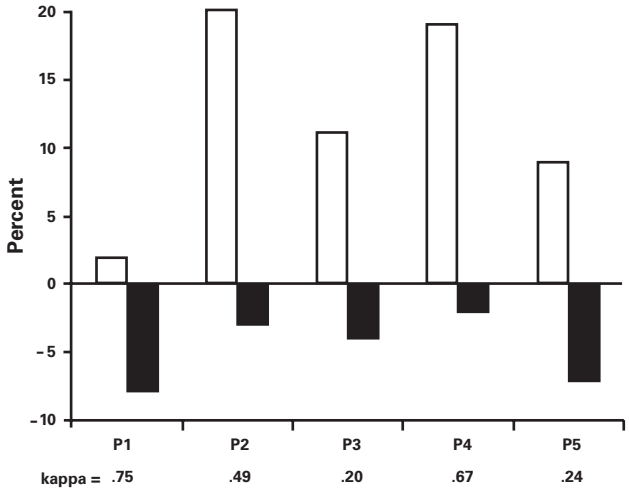


**Figure 1** Discrepancy trends and kappa. White columns, overdiagnosis; black columns, underdiagnosis. P, pathologist.

**Table 7**
**Percentage of Agreement in Interpretation of Biopsy Specimens Obtained for ASCUS vs LSIL vs HSIL**

| | ASCUS | LSIL | HSIL |
|---|---|---|---|
| 5/5 | 24 | 23 | 65 |
| 4/5 | 19 | 50 | 18 |
| 3/5 | 38 | 18 | 12 |
| 1-2/5 | 19 | 9 | 6 |
| | 100 | 100 | 100 |

ASCUS, atypical squamous cells of undetermined significance; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.

HSIL. Of the 22 biopsy specimens obtained for a cytologic diagnosis of LSIL, 2 had no consensus diagnosis, 6 were benign, 12 were LSIL, and 2 were HSIL. Of the 17 biopsy specimens obtained for a cytologic diagnosis of HSIL, 1 had no consensus diagnosis, 1 was benign, 3 were LSIL, and 12 were HSIL. Interobserver agreement in interpretation was better for the biopsy specimens obtained for a cytologic diagnosis of HSIL compared with those obtained for a cytologic diagnosis of LSIL which, in turn, was better than agreement for interpretation of specimens obtained for a cytologic diagnosis of ASCUS. This was reflected in both the ICC values and percentage of cases in full and partial agreement (Tables 7 and 8). The interobserver agreement was good for interpretation of the biopsy specimens obtained for HSIL (ICC, 0.61), fair for those obtained for LSIL (ICC, 0.40), and poor for those obtained for ASCUS (ICC, 0.25). All 5 pathologists agreed on the diagnosis for 65% of biopsy specimens obtained for HSIL, more than twice the rate for those obtained for ASCUS or LSIL. Conversely, failure to reach consensus was 3 times greater for the biopsy specimens obtained for ASCUS than those obtained for HSIL.

**Table 8**
**Intraclass Correlation Coefficient (ICC) for 60 Biopsy Specimens Obtained for ASCUS vs LSIL vs HSIL**

| Cytologic Diagnosis | No. of Biopsy Specimens | ICC | Interpretation |
|---|---|---|---|
| ASCUS | 21 | 0.25 | Poor |
| LSIL | 22 | 0.40 | Fair |
| HSIL | 17 | 0.61 | Good |

ASCUS, atypical squamous cells of undetermined significance; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.

**Table 9**
**Intraobserver Variance: Interpretation of 19 Biopsy Specimens Obtained for Atypical Squamous Cells of Undetermined Significance**

| Pathologist | kappa | Interpretation |
|---|---|---|
| 1 | 0.75 | Excellent |
| 2 | 0.49 | Fair to good |
| 3 | 0.20 | Poor |
| 4 | 0.67 | Good |
| 5 | 0.24 | Poor |

The intraobserver agreement in the interpretation of biopsy specimens obtained for ASCUS, using a weighted kappa statistic, ranged from 0.20 to 0.75, representing poor to excellent intraobserver agreement. The kappa values did not correlate with the discordant rate or diagnostic trends. The kappa values were highest for pathologists 1 and 4, who had very different tendencies; pathologist 1 was the most conservative in interpretation, and pathologist 4 was one of the most aggressive (Figure 1).

## Discussion

Four principal observations and conclusions can be drawn from this study: (1) Even among experienced pathologists, interobserver agreement is poor in the interpretation of cervical biopsy specimens obtained for follow-up of the cytologic diagnosis of ASCUS. (2) The interobserver agreement is worse for biopsy specimens obtained for ASCUS compared with those obtained for LSIL or HSIL, and it is better at the ends of the diagnostic spectrum than when the consensus diagnosis for the biopsy specimen is LSIL. (3) Intraobserver agreement in the interpretation of biopsy specimens obtained for ASCUS ranges from poor to excellent. (4) The high degree of interobserver variance contributes substantially to the reported differences in frequency of dysplasia following a cytologic diagnosis of ASCUS.

While at first glance a 92% consensus rate may appear good, the overall interobserver agreement in the interpretation of biopsy specimens obtained for ASCUS, as measured

by the ICC, was poor (0.34). The degree of interobserver agreement was related to the consensus diagnosis for the biopsy specimen. That is, the interobserver agreement was better when the consensus diagnosis was benign or HSIL than when the consensus diagnosis was LSIL. These findings are similar to those of Robertson et al,[14] who had 12 consultant pathologists examine 100 cervical biopsy specimens and classify the lesions into 1 of 7 categories: normal, inflammatory, immature squamous metaplasia, cervical intraepithelial neoplasia (CIN) 1, CIN 2, CIN 3, or "CIN 3 and possible invasion." They found poor overall interobserver agreement, fair agreement for benign diagnoses, poor agreement for CIN 1 and CIN 2, and good agreement for the category of CIN 3 and possible invasion. They found very poor agreement in the identification of human papillomavirus (HPV) changes. In a series of 3 studies by de Vet et al,[15] "considerable disagreement" was found when 4 experienced pathologists placed 106 cervical biopsy specimens into 1 of 5 diagnostic categories (unweighted kappa, 0.28; weighted kappa, 0.56). Agreement improved significantly when the same 4 pathologists diagnosed cervical biopsy specimens using 6 specific, agreed-on criteria (unweighted kappa, 0.33; weighted kappa, 0.70)[18] and when they met at a multiheaded microscope before the study to agree on the method for grading the biopsy specimens (unweighted kappa, 0.41; weighted kappa, 0.71).[19]

For the 5 pathologists in the present study, the rates of dysplasia in the follow-up of ASCUS ranged from 23% to 51% (Table 5). This range is similar to the range of 13.5% to 61.3% found in the literature for the rate of dysplasia in follow-up of ASCUS.[4,5,7,8,20] Our data support the hypothesis that interobserver variance in the interpretation of the biopsy specimen has an important role in the wide range of rates of dysplasia reported for the follow-up of ASCUS. In our study, all 5 pathologists agreed on the diagnosis in only 28% of cases, 4 agreed in an additional 36%, and 3 agreed in an additional 27%. In other words, at least 2 of the 5 pathologists disagreed with the consensus diagnosis (or no consensus was achieved) for one third of the biopsy specimens obtained for ASCUS.

Although in our initial set of cervical biopsy specimens interobserver agreement for HSIL was statistically "good," for 10 of 124 cases there were disagreements in interpretation among the 5 pathologists that ranged from one of the benign (ie, non-SIL) diagnoses to HSIL. Nine cases had a consensus diagnosis of HSIL, but for 23 cases (18.5%), at least 1 of the 5 pathologists interpreted the biopsy specimen as HSIL. The HSIL rate for each pathologist varied from 7% to 10%, a difference of 43%. Even more striking is the greater than 3-fold difference in LSIL rates among the 5 pathologists, from 13% to 41%. Clearly, different thresholds exist for the diagnosis of mild dysplasia/koilocytosis/HPV changes in cervical biopsy specimens, and the interface between LSIL and benign diagnoses is the most frequent and problematic. On the other hand, the interfaces between HSIL vs LSIL and HSIL vs benign, while less frequent, are of greater clinical importance for the patient and pathologist.

In our study, we used 5 experienced anatomic pathologists who have worked together closely for 5 or more years and often share cases that are diagnostically challenging. Therefore, we believe that, if anything, this study underestimates the interobserver variance in the interpretation of biopsy specimens obtained for ASCUS, across the United States and around the world.

The intraobserver variance in the interpretation of biopsy specimens obtained for ASCUS (based on 19 cases) ranged from poor to excellent. Interestingly, the 2 pathologists with the highest internal agreement (pathologists 1 and 4) had very different tendencies in their interpretation: pathologist 1 was the most conservative (ie, benign diagnoses) of the group, and pathologist 4 was among the most aggressive in calling SIL (Figure 1). This highlights the fact that intraobserver variance is a measure of precision, not accuracy.

Despite its long history, with such poor interobserver and intraobserver agreement, cervical biopsy does not represent a good gold standard for the follow-up of ASCUS. This raises the question of what might provide a better gold standard. For example, one might consider HPV detection and typing, expert consultation, or adjunctive studies (eg, cell proliferation markers). Each has its assets and proponents, yet none represents a reliable and cost-effective gold standard to be implemented on a wide scale, at least at the present. HPV testing has been shown to be of value for resolving cases that are equivocal by H&E staining,[21] but widespread use to resolve all equivocal cases still awaits acceptance in the West and is impractical in underdeveloped countries.

The rate of indeterminate epithelial atypia (benign vs SIL) ranged among the 5 pathologists from 0% to 14%. The reproducibility for this diagnosis was poor (ICC, –0.01). Nevertheless, the high level of interobserver disagreement in the interpretation of cervical biopsy specimens obtained for ASCUS and a rate of indeterminate from 0% to 14% suggest that a biopsy diagnosis of "epithelial atypia, benign vs SIL" may be appropriate in some cases, and such an interpretation should perhaps be codified in surgical pathology. Prasad et al,[21] in examining 37 cervical biopsy specimens, found support for a category of "nondiagnostic squamous atypia." Creating a surgical pathology equivalent of ASCUS may be unattractive to pathologists who are reluctant to admit doubt or gynecologists who have to determine appropriate treatment for patients with such a diagnosis. However, it may most accurately reflect the state of our art in interpreting the

routine H&E-stained slide in an important minority of cases. Recently, the reality of diagnostic uncertainty has been recognized similarly in biopsy specimens of other organs such as prostate ("ASAP"), although not without controversy.[22] Interobserver variance and diagnostic uncertainty are part of our reality; communicating that reality is our obligation to the clinician and the patient. Our findings also raise important questions about the litigation of cases in which atypical squamous cells go undetected or misinterpreted. With poor interobserver agreement in interpretation of both the Pap smear and any subsequent biopsy specimen that might have been obtained for ASCUS, the burden of proving negligence becomes more difficult.

The difficulties encountered in interpreting atypical squamous cells in cervical smears are paralleled in the subsequent biopsy specimens. Because of high interobserver and intraobserver variance in its interpretation, the cervical biopsy specimen should not be considered a gold standard for evaluating women with ASCUS. Further work is needed to find a better, yet cost-effective alternative. Interobserver variance in the interpretation of cervical biopsy specimens has an important role in the differences in rate of dysplasia reported for the follow-up of ASCUS. Subsequent studies examining the follow-up of ASCUS should take this into account.

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