False-Negative Interpretation of Adenocarcinoma In Situ in the College of American Pathologists Gynecologic PAP Education Program

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• ***Context.***—**Adenocarcinoma in situ (AIS) is difficult to correctly interpret on Papanicolaou (Pap) cytology slides and false-negative interpretations of AIS can cause significant problems in daily practice.**

Objective.—**To investigate the false-negative interpretation rate of AIS and the factors related to false-negative interpretation through responses in an educational environment.**

Design.—**We retrospectively evaluated 11 337 responses in the PAP Education Program (PAP-Edu) from 173 AIS slides from 2011 to 2015. The false-negative interpretation rate, most common false-negative interpretations, and related other factors were evaluated.**

Results.—**The overall false-negative rate was 6.9% (784 of 11 337). Respondents correctly interpreted AIS 50.0% (5667 of 11 337) of the time; high-grade intraepithelial lesion (HSIL) and malignancies (adenocarcinoma, squamous cell carcinoma, and other carcinomas) accounted for 42.7% (4842 of 11 337) and low-grade intraepithelial lesion accounted for 0.4% (44 of 11 337) of responses. Overall, 92.7% (10 509 of 11 337) of responses were HSIL and above. Among 784 false-negative responses, negative for intraepithelial lesion or malignancy was the most common (61.5% [482 of 784]), followed by reparative changes (24.1% [189 of 784]) and atrophic vaginitis (7.7% [60 of 784]). Overall, pathologists' responses showed a significantly higher false-negative rate than cytotechnologists' responses (8.3%, 403 of 4835 versus 5.7%, 275 of 4816; $P < .001$). The false-negative response rates were not statistically different among preparation types.**

Conclusions.—**The low correct interpretation rate and higher false-negative rate for AIS demonstrate the difficulty in interpreting AIS on Pap cytology, which may cause clinical consequences. The higher false-negative rate with pathologists than with cytotechnologists suggests cytotechnologists' higher screening sensitivity for AIS or cautious interpretation to avoid false-positive results by pathologists.**

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Cervical glandular neoplasia, including adenocarcinoma in situ (AIS) and invasive adenocarcinoma, is less common than squamous neoplasia. However, the relative proportion of glandular neoplasia has increased from 5% to 25% of all cervical cancer diagnoses in the United States during the past few decades.[1] Adenocarcinoma in situ is the precursor of invasive cervical adenocarcinoma and early management will often prevent the occurrence of invasive adenocarcinoma.[2] There is an interval of at least 5 years between clinically detectable AIS and invasive disease for most cases, suggesting ample opportunity for screening and intervention.[3,4]

Histologically, AIS is characterized by endocervical glands that exhibit a crowded or cribriform pattern and are lined with atypical pseudostratified columnar epithelial cells. Mitoses are commonly present in the glands and the amount of cellular cytoplasm is decreased. By definition, stromal invasion is absent but can be difficult to assess histologically. Patients with AIS are nearly always asymptomatic and the lesions are generally not visible upon gross examination.

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Table 1. Overall Interpretations of Adenocarcinoma In Situ (AIS)

Categories	No. of Responses	Percentage
AIS	5667	50.0
Adenocarcinoma	3571	31.5
HSIL	762	6.7
HSIL/carcinoma/carcinoma, NOS	431	3.8
Squamous cell carcinoma	67	0.6
Nonepithelial malignancy	11	0.1
LSIL	44	0.4
Negative	784	6.9
Total	11 337	100

Abbreviations: HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; NOS, not otherwise specified.

Cytologically, typical AIS cells are in groups and strips with rosette formation, feathering, crowding and/or stratification with indistinct cell borders. The nuclei are described as "cigar shaped" or elongated in most cases and nucleoli are inconspicuous. The nuclear to cytoplasmic ratio is increased. However, these characteristic features are not always present. Papanicolaou (Pap) cytology detects only 38% to 50% of AIS cases, indicating that cytology alone often is ineffective for detecting AIS.[5–7] This low detection rate is caused not only by sampling difficulty because of the location of AIS within the endocervical canal,[8,9] but also by an inability to recognize AIS on Pap slides.[10] Either glandular or squamous cytologic abnormalities may precede a histologic diagnosis of AIS and include glandular abnormalities (50%–69%), squamous abnormalities (26%–31%), mixed squamous and glandular abnormalities (15%), and negative cytologic results (4%).[11,12] About 1.1% to 4.7% of women with atypical glandular cells on cervical cytology have a histologic diagnosis of AIS at follow-up.[13–19] Liquid-based cytology has not improved the ability to accurately predict AIS.[20]

Since 1988, the College of American Pathologists (CAP) has been providing educational gynecologic cytology glass slide challenges through the Interlaboratory Comparison Program in Cervicovaginal Cytology (PAP program).[21] In 2006, the CAP, in response to an emerging need in the cytology community for additional Centers for Medicare & Medicaid Services–approved and well-validated proficiency programs, transformed the PAP program into 2 separate but interrelated programs: PAP Education Program (PAP-Edu) and PAP Proficiency Test Program (PAP-PT). PAP-Edu provides laboratories performing gynecologic cytology an option to meet the CAP Laboratory Accreditation Program Phase I requirement of enrollment in an educational interlaboratory comparison program. As noted above, it is difficult to specifically recognize AIS on Pap slides. In earlier studies of PAP-Edu, significantly more AIS Pap slides were interpreted as negative than as other significant lesions including high-grade squamous intraepithelial lesion (HSIL), squamous cell carcinoma, and adenocarcinoma.[10] The false-negative rate for AIS has been reported as 3.8% to 11.7%.[10,12,22] The high false-negative interpretation rate for AIS is an important problem in daily practice. The aim of this study was to investigate the false-negative interpretation of AIS and the factors related to false-negative interpretations through responses in an educational environment by analyzing the responses to AIS Pap slides in the PAP-Edu program.

MATERIALS AND METHODS

Participants in the PAP-Edu program and members of the CAP Cytopathology Committee contribute slides to the programs. Submitted slides with a diagnosis of HSIL, AIS, or higher must be confirmed by subsequent or concurrent biopsy. The slides and accompanying clinical information are reviewed and agreed upon by a minimum of 3 anatomic pathology board-certified members of the CAP Cytopathology Committee. PAP-Edu slides that become field validated can be used for PAP-PT slide sets; however, AIS cases currently remain in PAP-Edu sets.[23–25] In both PAP-Edu and PAP-PT programs, the interpretive menu includes selection categories A, B, C, and D. PAP-Edu directs participants to specifically choose category D subcategories that include HSIL, AIS, squamous cell carcinoma, adenocarcinoma–not otherwise specified (NOS), HSIL/carcinoma and/or carcinoma-NOS, and nonepithelial malignant neoplasm. However, the category D in PAP-PT has participants select only 1 option, HSIL and above.

We retrospectively analyzed 11 337 responses from 173 AIS slides that were reported in the CAP PAP-Edu program between 2011 and 2015. The 173 slides included 164 liquid-based preparation slides, including 135 ThinPrep slides (Hologic, Bedford, Massachusetts) and 29 SurePath slides (BD Diagnostics, Franklin Lakes, New Jersey), and 9 conventional preparation slides. A misinterpretation response was defined as an AIS slide interpreted under a category other than AIS, while a false-negative response was defined as an AIS case undercalled as negative for intraepithelial lesion or malignancy (NILM)/benign. Unsatisfactory responses were very low, with fewer than 5 responses during the study period. These results were excluded from the analysis.

Our analysis examined the factors associated with the false-negative rate of the AIS slides. A nonlinear mixed model was fit by using 2 factors—participant type (pathologist versus cytotechnologist) and preparation type (ThinPrep versus SurePath versus conventional). The interaction term for these factors was also included in the model. There was no performance trend, so program year was not included in the model (Cochran-Armitage trend test; $P = .10$). The model included a repeated measures component to model the slide factor correlation structure, which controls for slide-specific performance. A significance level of .05 was used for this analysis. All analyses were run with SAS v9.3 (SAS Institute, Cary, North Carolina).

RESULTS

The overall responses to AIS slides among laboratories, pathologists, and cytotechnologists are summarized in Table 1. The correct interpretation rate of AIS slides was only 50.0% (5667 of 11 337). High-grade intraepithelial lesion, carcinomas, or malignant neoplasms accounted for 42.7% (4842 of 11 337) of responses and low-grade squamous intraepithelial lesion accounted for 0.4% (44 of 11 337). Among the responses of HSIL and invasive malignancies, adenocarcinoma was the most common interpretation, accounting for 73.8% (3571 of 4842). The overall false-negative rate was 6.9% (784 of 11 337). Overall, 92.7% (10 509 of 11 337) of responses were HSIL and above. We first analyzed the false-negative interpretation data by participant types and slide preparation types (Table 2). Overall, pathologists' responses showed a significantly higher false-negative rate than cytotechnologists' responses (8.3%, 403 of 4835 versus 5.7%, 275 of 4816; $P < .001$). The participant-type performance differences were significant for both ThinPrep (pathologist-cytotechnologist, $P < .001$) and SurePath preparations (pathologist-cytotechnologist, $P < .001$) (Table 2).

When the false-negative rates were compared among different preparations (ThinPrep, SurePath, and conventional), no significant difference was identified overall. The false-negative rate was highest for conventional prepara-

Table 2. Comparison of False-Negative Response Rate of Adenocarcinoma In Situ for Participant Types and Preparation Types–Nonlinear Mixed Model Summary[a]

Factors	No. of Responses	False-Negative, No. (%)	*P* Value
Participant type			<.001
Pathologist	4835	403 (8.3)	
Cytotechnologist	4816	275 (5.7)	
Laboratory	1686	106 (6.3)	
Preparation type			.36
ThinPrep[b]	9619	636 (6.6)	
SurePath[c]	1531	124 (8.1)	
Conventional	187	24 (12.8)	
Participant type[a] and preparation type			.07
ThinPrep[b]			
Pathologist	4117	317 (7.7)	
Cytotechnologist	4105	232 (5.7)	
Laboratory	1397	87 (6.2)	
SurePath[c]			
Pathologist	653	76 (11.6)	
Cytotechnologist	645	37 (5.7)	
Laboratory	233	11 (4.7)	
Conventional			
Pathologist	65	10 (15.4)	
Cytotechnologist	66	6 (9.1)	
Laboratory	56	8 (14.3)	

[a] Significant test results: Pathologist-cytotechnologist ($P=.002$); no testing for laboratory participants; Thin Prep: pathologist-cytotechnologist ($P < .001$); SurePath: pathologist-cytotechnologist ($P < .001$).
[b] Hologic, Bedford, Massachusetts.
[c] BD Diagnostics, Franklin Lakes, New Jersey.

tions (Table 2), but not significantly different. This is likely due to the small number of responses for conventional slides, which may affect the analysis. In addition, cytotechnologists had more AIS interpretations than pathologists in both ThinPrep (53.0%, 2175 of 4105 versus 47.6%, 1960 of 4117) and SurePath slides (50.1%, 323 of 645 versus 44.6%, 291 of 653).

In the PAP-Edu program, category B (negative) allows participants to select several responses: NILM with no additional descriptors, fungal organisms consistent with *Candida* spp, *Trichomonas vaginalis*, cellular changes consistent with herpes simplex virus, reparative cytologic changes, atrophic vaginitis, and follicular cervicitis. The false-negative frequency distributions are summarized in Table 3. Among 784 false-negative responses, NILM was the most common, accounting for 61.5% (482 of 784), followed by reparative changes (24.1%, 189 of 784) and atrophic vaginitis (7.7%, 60 of 784).

The distributions of false-negative interpretation were further analyzed by the preparation types and participant types (Tables 3 and 4). Adenocarcinoma in situ was more frequently interpreted as atrophic vaginitis on SurePath than on ThinPrep slides, but less frequently interpreted as NILM or reparative changes (Table 3). When the distributions were further stratified by participant types (pathologist, cytotechnologist, and laboratory), no significant difference among the different false-negative interpretation was identified among these 3 participant types (Table 4).

DISCUSSION

Adenocarcinoma in situ is difficult to specifically recognize on Pap slides and the false-negative interpretation rate is significantly higher for AIS than that for other significant lesions including HSIL, squamous cell carcinoma, and adenocarcinoma.[10] To our knowledge, this is the largest study to investigate the false-negative interpretation rate for AIS. The false-negative interpretation rate for AIS from our study was 6.9%, which is within the reported range of 3.8% to 11.7%.[10,12,22]

Table 3. Specific Negative Participant Interpretations for Adenocarcinoma In Situ Slides by Preparation Types

Participant Interpretation	Total, No. (%)	Conventional, No. (%)	ThinPrep,[a] No. (%)	SurePath,[b] No. (%)
NILM	482 (61.5)	16 (66.7)	400 (62.9)	66 (53.2)
Reparative changes	189 (24.1)	7 (29.2)	158 (24.8)	24 (19.4)
Atrophic vaginitis	60 (7.7)	0 (0.0)	41 (6.4)	19 (15.3)
Trichomonas vaginalis	21 (2.7)	1 (4.2)	13 (2.0)	7 (5.6)
Fungal organisms consistent with *Candida* spp	15 (1.9)	0 (0.0)	12 (1.9)	0 (0.0)
Cellular changes consistent with herpes simplex virus	12 (1.5)	0 (0.0)	8 (1.3)	7 (5.6)
Follicular/lymphocytic cervicitis	5 (0.6)	0 (0.0)	4 (0.6)	1 (0.8)
Total	**784**	**24**	**636**	**124**

Abbreviation: NILM, negative for intraepithelial lesion or malignancy.
[a] Hologic, Bedford, Massachusetts.
[b] BD Diagnostics, Franklin Lakes, New Jersey.

Table 4. Negative Participant Interpretations for Adenocarcinoma In Situ Slides by Participant Types			
Participant Interpretation	**Cytotechnologist, No. (%)**	**Pathologist, No. (%)**	**Laboratory, No. (%)**
NILM	171 (62.2)	248 (61.5)	63 (59.4)
Reparative changes	62 (22.5)	97 (24.1)	30 (28.3)
Atrophic vaginitis	26 (9.5)	27 (6.7)	7 (6.6)
Cellular changes consistent with herpes simplex virus	7 (2.5)	6 (1.5)	2 (1.9)
Trichomonas vaginalis	6 (2.2)	12 (3.0)	3 (2.8)
Fungal organisms consistent with *Candida* spp	2 (0.7)	9 (2.2)	1 (0.9)
Follicular/lymphocytic cervicitis	1 (0.4)	4 (1.0)	0 (0.0)
Total	**275**	**403**	**106**

Abbreviation: NILM, negative for intraepithelial lesion or malignancy.

In the current study, AIS was specifically recognized by only 50.0% of participants, which was similar to the previously reported result from PAP programs.[10] Many AIS slides were misinterpreted as HSIL or malignancy, indicating the difficulty in distinguishing AIS from HSIL, squamous cell carcinoma, and especially adenocarcinoma, based on cytomorphologic features alone. Clinically, misinterpretation of an AIS Pap as HSIL or other malignancy would not cause a significant impact on the management of the patient, because patients with any of these diagnoses will undergo colposcopy and biopsy. However, misinterpretation of AIS Pap test as a negative result may result in serious clinical and medicolegal consequences unless the patient also has a positive human papillomavirus test result that leads to closer monitoring or evaluation. In the current study, we focused on investigating the false-negative responses and their related factors. The false-negative interpretation rate for AIS from our study was 6.9%, which was much higher than the false-negative interpretation rate for HSIL (0.9%) in the CAP PAP-Edu program reported in our recent study.[26] The false-negative rate for AIS Pap slides was reported to be as high as 11.7% in PAP programs previously.[10] The current results may indicate that the participants of the PAP-Edu program have improved on the interpretation of AIS over time. However, the slides used in the 2001 and 2002 CAP Interlaboratory Comparison Program in Cervicovaginal Cytology Program were conventional preparations and did not include liquid-based preparations. The false-negative rate for HSIL reported in that study was also much higher than what we found in our recent study (4.6%, 343 of 7535 versus 0.9%, 266 of 28 000).[10,26]

Glandular cell abnormalities in the Bethesda System include atypical endocervical cells; atypical endometrial cells; atypical glandular cells, not otherwise specified; atypical endocervical (or glandular) cells, favor neoplastic; AIS; and adenocarcinoma of various types. The atypical glandular and squamous categories are excluded in both the CAP PAP-Edu and PAP-PT program because of interobserver variability and lack of a gold standard biopsy correlation. The difference of reporting categories between daily practice and the PAP-Edu program may affect the false-negative rate of AIS in the PAP-Edu program.

In this study, we also analyzed the potential factors related to false-negative interpretations, including preparation types and participant types. Pathologists' responses showed a significantly higher false-negative rate than cytotechnologists' responses (8.3% versus 5.7%, $P < .001$) in both ThinPrep and SurePath preparations, indicating that cytotechnologists had higher sensitivity for AIS, possibly owing to their job emphasis on highly sensitive screening skills. Pathologists are responsible for the final interpretation and may be less likely to commit to a definitive AIS interpretation. The participants' attitude toward the PAP-Edu program may also contribute to the different false-negative rates between pathologists and cytotechnologists. Cytotechnologists might review the slides more carefully than pathologists and may be more likely than pathologists to have PAP-Edu results used as a part of their competency evaluation.

Our study showed that when the false-negative rates were compared among different preparations (ThinPrep, SurePath, and conventional), no significant difference was identified overall. ThinPrep slides overall had the lowest false-negative rates; however, numbers of participant responses for conventional slides (187 of 11 337; 1.6%) were too low to demonstrate statistical differences. Roberts and Thurloe[20] reported that liquid-based cytology implementation had not improved the ability to accurately predict AIS. Liquid-based preparations tend to cause cell groups to round up, and feathering can be difficult to assess in liquid-based preparations as opposed to conventional preparations. One recent study[27] evaluated the detection rate of glandular lesions (both AIS and adenocarcinoma) and found that the false-negative rate for Pap tests to detect glandular lesions was 8.8%. They further analyzed discordance scores among different methodologies and found that SurePath nonimaged cases had the lowest discordance score (0.2), followed by ThinPrep nonimaged cases (1.1), ThinPrep imaged cases (1.4), and conventional cases (1.6). However, the number of cases in this study was quite small with a total of 91 cases.[27] The discrepancy between our study and the previous study may result from many factors, such as quantitative and obscuring artifact differences among individual cases, staining variation secondary to preparatory techniques, and cytopathologists' comfort level with the various preparations. Therefore, further studies are warranted to compare performance of these different methods, not only for AIS, but also for other glandular abnormalities.

Among all false-negative responses, NILM with no other descriptors was the most common, accounting for 61.5% (482 of 784), followed by reparative changes (24.1%, 189 of 784), and atrophic vaginitis (7.7%, 60 of 784). All other negative categories including microorganisms accounted for only 6.8% (53 of 784) of the false-negative responses. These findings suggest that the main reasons for the false-negative interpretations were that AIS cells were either not identified or were misinterpreted as reactive or reparative changes. In daily practice situations, cytotechnologists and pathologists may choose to classify cases they perceive as not having classic AIS criteria as "atypical" to prompt further investigation.

In conclusion, the low correct interpretation rate and high false-negative rate for AIS reveals the difficulty in interpret-

ing AIS on all types of cytology preparations and reflects room for improvement in the interpretation of AIS. The significantly higher false-negative rate from pathologists than from cytotechnologists suggests that cytotechnologists have better Pap cytology screening skills. The higher false-negative rate in SurePath than in ThinPrep preparations warrants further studies to compare performance of these 2 methods.

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