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Preinvasive and Invasive Cervical Adenocarcinoma: Preceding Low-Risk or Negative Pap Result Increases Time to Diagnosis

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Abstract

Objectives—The aims of the study were to investigate screening histories of women with adenocarcinoma in situ (AIS) and adenocarcinoma (AdCa) of the cervix and to further evaluate screening for glandular disease.

Materials and Methods—Screening histories were retrospectively collected for patients with AIS or AdCa at a single large-volume academic institution from 2005 to 2015. Fisher exact and Wilcoxon rank sum tests were used to compare AIS with AdCa patient characteristics, distribution of preceding Pap (i.e., trigger Pap) results, and high-risk human papillomavirus testing. The association between Pap result and time to diagnosis was evaluated.

Results—Eighty-seven cases, 50 AIS and 37 AdCa, met study criteria; median age was 31 and 43 years, respectively. Among the AIS cohort, 52.0% had a negative or low-risk trigger Pap result versus 24.3% of those with AdCa ($p = .001$). The time to diagnosis of AIS ranged from 8.4 to 18.8 weeks for those with high- versus low-risk or negative trigger Pap results, respectively ($p = .002$). The time to diagnosis of AdCa ranged from 14.6 to 44.7 weeks for those with high- versus low-risk or negative trigger Pap results, respectively ($p = .003$). Among those with high-risk human papillomavirus testing, 89.7% tested positive at the time of trigger Pap with 100% positivity among those with low-risk or negative trigger Pap results.

Conclusions—Cervical AIS and AdCa affect many young nulliparous women and commonly preceded by low-risk or negative Pap testing. The interval to diagnosis increases with low-risk and negative Pap results, and therefore, further investigation into optimal screening for glandular lesions is needed.

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Keywords

cervical adenocarcinoma in situ; cervical adenocarcinoma; cervical cancer screening; human papillomavirus; pap smear; pap test; human papillomavirus

Cervical cancer screening in the United States using Pap test was implemented in the 1950s and has been credited with an approximately 80% reduction in the nationwide incidence of and mortality from cervical cancer. Although this screening test has dramatically decreased the incidence of cervical cancer overall, this reduction is largely due to successful detection of preinvasive squamous lesions. On the other hand, the incidence of adenocarcinoma (AdCa) of the cervix has, in fact, increased in the United States in recent decades.^{1–5} In a population-based study using the SEER database (The Surveillance, Epidemiology, and End Results) from 1973 to 1996, the incidence of AdCa increased by 29.1%.³ Importantly, this increase in glandular disease is particularly prevalent in young women,^{6–9} with one study demonstrating that the incidence of glandular lesions in women aged 20 to 34 years had tripled from 1970 to 1996.⁹

Although most research on cervical cancer screening has focused on when and how squamous lesions are missed, fewer studies have investigated Pap test as a screening tool for AdCa and adenocarcinoma in situ (AIS). A 10-year retrospective study by Zhao et al¹⁰ demonstrated that 61% of women with glandular lesions of the cervix were found to have only negative cytology within the 3 years before their diagnosis; however, 97% of patients tested positive for human papillomavirus (HPV). Additional studies have also suggested improved detection of glandular lesions with HPV testing over the Pap test alone.¹¹ Although current screening guidelines have begun to incorporate co-testing with the HPV test, they continue to allow Pap testing alone in women aged 31 to 65 years, and national society guidelines recommend Pap testing alone for women younger than 30 years.¹² Because the incidence of AdCa and its precursor AIS continue to rise, additional investigation of Pap test as an adequate screening test for glandular lesions of the cervix is necessary.

Therefore, our study objective is to further evaluate Pap test as a screening test for atypical endocervical glandular lesions by investigating the interval from Pap test immediately before AIS and AdCa diagnosis (i.e., the trigger Pap test) to date of diagnosis of preinvasive or invasive glandular disease.

MATERIALS AND METHODS

This was a retrospective cohort study of women with cervical AIS and AdCa, diagnosed during a 10-year period between January 1, 2005, and January 1, 2015, at a single large-volume, academic institution. After obtaining approval from the institutional review board of Johns Hopkins Hospital (JHH, Baltimore, MD), a computer-based search of the pathology database was carried out to identify histopathologically confirmed cases of cervical AIS or AdCa. Retrospective chart review was then performed to obtain patient demographic information, cervical pathology, and cervical cancer screening history. Demographic information included age, race, parity, body mass index, smoking status, HIV status, and

presence of comorbidities. Comorbidities included diabetes mellitus, polysubstance abuse, hypertension, autoimmune disease, and hepatitis. Clinical findings such as bleeding or visually noted cervical lesions on speculum examination were recorded. For those cases in which the clinical findings prompted the diagnostic work-up, the cervical cancer screening results were still documented when available.

Cervical cancer screening histories for each patient in the cohort were collected, including all Pap test screening and HPV testing results. The trigger Pap was defined as a Pap test performed immediately before diagnosis of AIS or AdCa. Cytologic test results were mostly rendered by cytopathologists at JHH, whereas the remainder were performed by cytopathologists at outside institutions. In addition, a significant portion of those obtained outside the JHH system were reviewed by JHH pathologists. The combination of testing performed at JHH and cases reviewed by a JHH cytopathologist encompasses more than 98% of the cases. Pap test results were categorized as preinvasive/carcinoma, high risk, low risk, or negative intraepithelial lesion or malignancy (NILM). The preinvasive/carcinoma category included AIS, adenosquamous carcinoma (AdsqCa), and AdCa. Pap test results including high-grade squamous intraepithelial lesion (HSIL) and atypical glandular cells (AGCs) were classified as high risk, whereas low-grade squamous intraepithelial lesion (LSIL) and atypical squamous cells of undetermined significance (ASCUS) were classified as low risk. This grouping was determined given that ASCUS and LSIL lesions have a greater risk of regression and lower risk of development into invasive cancer when compared with HSIL and AGC.^{13,14} Pap tests received at JHH were processed and collected using BD SurePath (BD, Franklin Lakes, NJ). All cytology results were reported using the 2014 Bethesda System (TBS).¹⁵

Human papillomavirus testing results were obtained through JHH high-risk HPV DNA testing using the US Food and Drug Administration–approved Hybrid Capture 2 assay (HC2; Quagen, Germantown, Md), which tests for high-risk and intermediate-risk HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. The results of the test were reported as positive, negative, or equivocal.

The diagnosis of AIS or AdCa was established from Pap test or histopathologic specimens obtained by endocervical curettage, cervical biopsies, loop electrosurgical excision procedures, cold-knife cervical conization, or hysterectomy. Gynecologic subspecialty pathologists at JHH reviewed all histologic specimens.

The interval between the trigger Pap and the histopathologic diagnosis of AIS or AdCa was calculated in weeks, using the exact dates of diagnosis when available. For those cases in which the exact date was not available, the first of the identified month was used. All pregnant women were excluded from this analysis. Any patients with missing data of specific Pap test results or date of Pap test diagnosis were also excluded from this analysis.

Summary statistics are provided as mean (SD) or median (interquartile range or range) as noted. The Fisher exact test was used to compare the distribution between groups for categorical variables, whereas the Wilcoxon rank sum was used for continuous variables when comparing AdCa and AIS patient characteristics, distribution of preceding trigger pap,

and the impact of hrHPV-positive testing on time to diagnosis. The Conover-Iman test with Hochberg (post hoc multiple comparisons) was used to compare more than two groups when analyzing time from preceding Pap test to diagnosis. The analyses were conducted using STATA Version 14.1 (Stata Corporation, College Station, Tex). A p value of less than .05 was considered statistically significant.

RESULTS

From the pathology database, 117 patients were identified with diagnoses of AIS ($n = 54$, 46%) and AdCa ($n = 63$, 54%). Of the 117 cases, 87 (75%) had sufficient data available at time of trigger Pap to be included for analysis, with 50 cases of AIS (57%) and 37 cases of AdCa (43%). The remaining 30 cases with insufficient information were excluded, as outlined in Figure 1.

For the 87 women included in the final cohort, the median age was 35 years (range = 18–70 years) and median body mass index was 26 kg/m² (range = 18–50 kg/m²). Seventy-two percent of women were white and 15% were African American. Forty-seven percent of women were nulliparous, 83% were nonsmokers, and 52% had no major comorbidities. When comparing the AdCa cohort with the AIS cohort, demographic characteristics were similar, other than age and parity. Women diagnosed with AIS were noted to be significantly younger, with a median age of 31 years, compared with those diagnosed with AdCa at a median age of 43 ($p < .001$). In addition, women with AIS were more likely to be nulliparous, 59% versus 32% ($p = .02$, see Table 1).

Cervical Cancer Screening Results

In the overall cohort, a low-risk/negative trigger Pap was as prevalent as a high-risk trigger Pap (40.0% vs 43.7%, respectively). Among 35 women with low-risk or negative trigger Pap results, 8 (9.2%) had LSIL, 16 (18.4%) ASCUS, and 11 (12.6%) NILM. Among 38 women with high-risk results, 16 (18.4%) had HSIL and 22 (25.3%) had AGC. The remaining 14 women (16.1%) had preinvasive or invasive carcinoma diagnosed on the trigger Pap. Upon comparing differences in trigger Pap test results in women diagnosed with AdCa versus AIS, patients with AIS were more likely to have a low risk or negative trigger Pap than patients diagnosed with AdCa (52% vs 24.3%, $p < .001$, see Table 2).

Results of hrHPV testing at the time of the trigger Pap testing were available for 39 (44.8%) of the 87 cases. Of note, those missing high-risk HPV (hrHPV) testing data were either younger than 30 years ($n = 17$), not requested by outside provider ($n = 1$), or progressed to invasive glandular lesions before the introduction of routine HPV co-testing for women older than 30 years ($n = 30$). Thirty five (89.7%) of 39 women tested positive for hrHPV at time of trigger Pap. Five of 6 women with carcinoma or AIS on trigger Pap tested positive for hrHPV (83%), 11 (79%) of 14 women with high-risk results on trigger Pap tested positive for hrHPV, and all 19 women (100%) with low-risk or negative trigger Pap results tested positive for hrHPV (see Table 3).

Interval to Diagnosis

The time to histopathologic detection of an atypical endocervical glandular lesion varied on the basis of trigger Pap test results. The interval ranged from an average of 11.1 weeks for those with high-risk results (HSIL or AGC) to 22.0 weeks for women with low-risk (LSIL or ASCUS) or negative trigger Pap results ($p < .001$). Of note, for those 11 women in whom trigger Pap was negative, further work-up leading to diagnosis was prompted mostly by positive HPV 16 or 18 genotyping. The remainder were 2 cases of persistent HPV-positive testing, a single case of a dilation and curettage performed for a thickened endometrial stripe, as well as a case of a cervical lesion visualized and biopsied during clinical examination.

Among the AIS and AdCa cohorts, the time to diagnosis differed by trigger Pap results. Among women with AIS, time to diagnosis was 8.4 weeks for those with high-risk results and 18.8 weeks if preceding Pap result was low risk or negative ($p = .003$). The mean time to AdCa diagnosis was 3.8 weeks for women with a trigger Pap test indicating AIS, 4.6 weeks for those with other high-risk Pap test results, and 18.8 weeks for those with low-risk or negative Pap testing ($p = .002$, see Figure 2).

Among 38 women with high-risk trigger Pap results, the time to diagnosis for those with no HPV testing was 11.7 weeks versus 10 weeks for those with HPV testing ($p = .29$). For the 24 women with low-risk trigger Pap results, the average time to diagnosis for those with Pap testing alone was 17.4 weeks versus 14.7 weeks for those with co-testing ($p = .57$, see Table 4).

DISCUSSION

Because the incidence of endocervical AdCa continues to increase nationwide, our understanding of this disease and the ability of current cervical cancer screening practices to detect glandular lesions becomes increasingly critical. Current screening guidelines, which have effectively exploited the pathogenesis of squamous cell carcinoma (SCC) of the cervix, have resulted in a tremendous decrease in the incidence of SCC; however, AdCa of the cervix differs from SCC in its distribution of HPV genotypes, associated risk factors, and prognosis.¹⁶ These distinctions suggest key differences in the biology of these histologic subtypes. Therefore, it is critical to understand the utility of the current screening tests for detection of glandular lesions and most importantly, to critically evaluate how the current screening guidelines impact the ability to detect AdCa and AIS.

In this retrospective cohort, most women (52%) diagnosed with AIS had low-risk or negative cervical cytological findings on the trigger Pap immediately preceding the AIS diagnosis, 10% of which were NILM, and all of which were HPV positive. The findings in this study are consistent with other studies that suggest a low sensitivity of Pap test as a screening tool for glandular lesions of the cervix.^{17–19} This diminished sensitivity of Pap test for glandular lesions can be explained by the tendency of AIS and AdCa to involve areas of the cervix that are difficult to sample, such as the endocervical canal. In addition, pathologists have reported that on cytology, AIS can resemble lower segment endometrial cells, endocervical cells with tubal metaplasia, as well as reactive endocervical cells. Consequently, they are

often mistaken for benign cells on cytology, further decreasing the sensitivity of Pap test for glandular lesions.^{20–22}

In this cohort, there was an inverse relationship between the severity of trigger Pap results and time to diagnosis, with up to a 9-month interval to diagnosis in women with NILM Pap results. Although the time to diagnosis did not differ significantly between those who did and did not have an HPV testing, these findings suggest that HPV testing may better reflect the risk of glandular lesions. These findings are especially important in the context of the current guidelines that recommend Pap testing alone as the only screening option for women up to the age of 30 years and permit Pap testing alone for women aged 31 to 65 years. Understanding how these guidelines affect our ability to detect glandular lesions and the time to diagnosis is critical, particularly in an increasingly young population with concerns for fertility conservation.

In this patient cohort, the median age of diagnosis of a cervical glandular lesion was 37, which is consistent with the age distribution reported in the SEER database,²³ and the peak incidence of AIS occurred at 31 years, consistent with previous studies.¹⁰ This earlier age of AIS diagnosis is not unexpected, given the pathogenesis of HPV disease. However, this gap in the natural history between preinvasive and invasive disease offers a significant opportunity for screening and early detection of glandular lesions, as well as a window for less aggressive interventions. A diagnosis of preinvasive versus invasive disease offers the opportunity for conservative fertility-preserving therapies, which are critically important to women in this age group. In addition, after having undergone a cold knife conization as an interim treatment to maintain fertility, cases have been reported of multicentric AIS with foci missed on cold knife conization.²⁴ It is crucial that there exists an effective screening method for these women after electing for this conservative option. Furthermore, with AdCa carrying a higher mortality rate than squamous carcinoma, this further stresses the importance of improving early detection of glandular lesions, specifically in this population of young women.²⁵

Consistent with other studies, we found a 90% presence of hrHPV in women with AdCa and AIS.^{26,27} Although the expanding knowledge of HPV and its integration into routine testing has resulted in increased sensitivity for glandular lesions,^{28,29} HPV co-testing alone is not sufficient to improve screening for glandular lesions. In women 30 years or younger, the American Society for Colposcopy and Cervical Pathology currently recommends Pap testing alone for cervical cancer screening because high HPV clearance rates and low specificity in this population. Therefore, particularly for those women with AIS (median age = 31 years), Pap test has poor sensitivity and HPV tests have low specificity. Therefore, optimal screening for glandular lesions in this population is limited. For women older than 30 years, where HPV positivity is more predictive of progressive dysplasias (both glandular and squamous disease), co-testing with hrHPV is beneficial for detection of glandular lesions. Although Pap testing alone currently remains an acceptable option for screening as per the American Society for Colposcopy and Cervical Pathology guidelines, findings from this and other studies, specific to glandular lesions, should be considered in evaluating the role of HPV testing in future screening algorithms. Furthermore, the role of HPV genotyping for triage of women with glandular lesions requires further investigation.

The conclusions drawn from this study are limited in that it is a retrospective analysis with a small sample size. In addition, patient access to follow-up impacts the time interval to diagnosis, which could not be adjusted for in this analysis. The years from which this study was conducted also represent a time when HPV screening was introduced, with changing recommendations; therefore, HPV status was not available on all women in this cohort. Lastly, there is a variation among providers who follow the Bethesda recommendations strictly, versus those who may vary their approach to these recommendations. Although these limitations were inevitable in this analysis, none should increase bias in the direction of the findings. Furthermore, this analysis has the added benefit of examining detailed and comprehensive screening histories to learn more about Pap test as a screening tool for glandular lesions of the cervix.

In conclusion, with additional data showing a yearly increase in rates of AdCa,²³ we must continue to revise and improve screening guidelines to reflect these epidemiologic changes. Screening for glandular lesions has historically fallen under the umbrella of SCC screening, and in this new age of individualized and genetic medicine, it is critical to recognize that this disease subtype is different from squamous disease and may require alternate screening methods and recommendations. As we continue to discuss screening paradigms with consideration for primary HPV testing, HPV genotyping, and further pathologic and molecular triage methods, the ability of each to detect glandular lesions of the cervix is of critical importance.

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FIGURE 1.
Database distribution by trigger Pap data availability.

Pap Result	AIS cases (n=48)		AdCa cases (n=30)		AdCa and AIS (n=78)	
	Preceding cytology, n	Weeks to diagnosis, mean (SD)	Preceding cytology, n	Weeks to diagnosis, mean (SD)	Preceding cytology, n	Weeks to diagnosis, mean (SD)
Carcinoma or in situ	2	0	9	0.84 (1.61)	11	0.69 (1.5)
High risk	21	8.4 (6.1)	16	14.6 (19.7)	37	11.1 (13.8)
Low risk or negative	25	18.8 (16.8)	5	44.7 (60.7)	30	22.0 (24.1)

FIGURE 2.

Time interval from preceding Pap test result to diagnosis of AdCa and AIS. This cohort was limited to those with available data on preceding cytology and weeks to diagnosis. High-risk category includes AGCs and HSIL. Low-risk category includes LSIL and ASCUS. Conover-Iman with Hochberg, post hoc multiple comparisons p value = .002 (AIS); p value = .003 (AdCa); p value < .001 (AdCa and AIS). 0 represents that the diagnosis was made at the time of trigger Pap.

TABLE 1

Demographic and Clinical Characteristics of AdCa and AIS Cases Among Final Cohort of 87 Patients

Characteristic	AdCa and AIS (<i>n</i> = 87)	AdCa (<i>n</i> = 37)	AIS (<i>n</i> = 50)	<i>P</i>
Age at diagnosis				
Median (range)	35 (18–70)	43 (24–70)	31 (18–56)	< .001
Body mass index, kg/m ²				
Median (range)	26 (18–50)	27 (18–50)	25 (19–43)	.05
Race or ethnicity, <i>n</i> (%) ^a				
White	63 (73.3)	24 (64.9)	39 (79.6)	.13
African American	13 (15.1)	9 (24.3)	4 (8.2)	
Asian	3 (3.5)	2 (5.4)	1 (2.0)	
Other	7 (8.1)	2 (5.4)	5 (10.2)	
Parity, <i>n</i> (%) ^a				
<i>p</i> = 0	41 (47.7)	12 (32.4)	29 (59.2)	.02
<i>p</i> = 1	45 (52.3)	25 (67.6)	20 (40.8)	
Smoking, <i>n</i> (%)				
Smoker	15 (17.2)	7 (18.9)	8 (16)	.78
Nonsmoker	72 (82.8)	30 (81.1)	42 (84)	
Comorbidities, <i>n</i> (%) ^b				
Present	42 (48.3)	20 (54)	22 (44)	.39
None	45 (51.7)	17 (46)	28 (56)	

Data presented as *n* (%), unless otherwise specified.

Analysis is by Wilcoxon rank sum and Fisher exact test based on type of characteristic being compared.

AdCa indicates adenocarcinoma; AIS, adenocarcinoma in situ.

^aSingle case of unknown race or ethnicity as well as parity.

^bComorbidities include diabetes mellitus, polysubstance abuse, hypertension, autoimmune disease, and hepatitis.

TABLE 2

Distribution of Glandular Lesions by Preceding Trigger Pap Test Result

Pap result	AdCa and AIS (<i>n</i> = 87)	AdCa (<i>n</i> = 37)	AIS (<i>n</i> = 50)
Carcinoma or in situ	14 (16.1)	12 (32.4)	2 (4.0)
AdsqCa	1 (1.1)	1 (2.7)	0
AdCa	7 (8.0)	7 (18.9)	0
AIS	6 (6.9)	4 (10.8)	2 (4.0)
High risk	38 (43.7)	16 (43.2)	22 (44.0)
AGC	22 (25.3)	10 (27.0)	12 (24.0)
HSIL	16 (18.4)	6 (16.2)	10 (20.0)
Low risk or negative	35 (40.2)	9 (24.3)	26 (52.0)
LSIL	8 (9.2)	1 (2.7)	7 (14.0)
ASCUS	16 (18.4)	2 (5.4)	14 (28.0)
NILM	11 (12.6)	6 (16.2)	5 (10.0)

Data presented as *n* (% of each cohort).

The bold values signify a sum of those sub-categories listed below.

Fisher exact test, $p = 0.001$, used to calculate the difference between the AdCa and AIS cohort regarding the distribution of Pap results by categories of carcinoma or in situ results, high-risk results, and low-risk or negative results.

AdCa indicates adenocarcinoma; AIS, adenocarcinoma in situ; AdsqCa, adenosquamous carcinoma; AGC, atypical glandular cells; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; ASCUS, atypical squamous cells of undetermined significance; NILM, negative intraepithelial lesion or malignancy.

TABLE 3Presence of hrHPV on HC2 at Time of Trigger Pap Testing^a

Pap result	hrHPV positive
Carcinoma or in situ	5/6 (83)
AdsqCa	1/1 (100)
AdCa	3/4 (75)
AIS	1/1 (100)
High risk	11/14 (79)
AGC	5/7 (71)
HSIL	6/7 (86)
Low risk or negative	19/19 (100)
LSIL	1/1 (100)
ASCUS	11/11 (100)
NILM	7/7 (100)
Total	35/39 (89.7)

Data presented as number of cases with hrHPV-positive results over total number of cases with hrHPV testing results available.

The bold values signify a sum of those sub-categories listed below.

hrHPV, high-risk human papillomavirus; HC2, hybrid capture2; AdsqCa, adenosquamous carcinoma; AdCa, adenocarcinoma; AIS, adenocarcinoma in situ; AGC, atypical glandular cells; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; ASCUS, atypical squamous cells of undetermined significance; NILM, negative intraepithelial lesion or malignancy.

Pap results categorized into carcinoma or in situ results, high-risk results, and low-risk or negative results.

^ahrHPV results available for 39 (44.8%) of the 87 cases.

TABLE 4
Impact of HPV on Time to Diagnosis Stratified by High- and Low-Risk Trigger Pap Results

Pap result	Pap alone (<i>n</i> = 36)		Pap and HC2 hrHPV (<i>n</i> = 25)		<i>P</i>
	Preceding cytology, <i>n</i>	Weeks to diagnosis, mean (SD)	Preceding cytology, <i>n</i>	Weeks to diagnosis, mean (SD)	
High risk	24	11.7 (17.3)	14	10.0 (4.6)	.29
Low risk	12	17.4 (10.5)	12	14.7 (8.3)	.57

These cohorts were limited to the cases with not only preceding cytology but also weeks to diagnosis data available.

High-risk category includes AGC and HSIL.

Low-risk category includes LSIL and ASCUS.

Comparison of distribution was performed with Wilcoxon rank sum test.

HC2 indicates hybrid capture2; hrHPV, high-risk human papillomavirus.