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ThinPrep Detection of Cervical and Endometrial Adenocarcinoma

A Retrospective Cohort Study

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BACKGROUND. The current study was performed to compare the accuracy of the ThinPrep™ Papanicoloau (Pap) test with that of the conventionally prepared Pap smear in detecting cervical and endometrial adenocarcinomas.

METHODS. The subject group consisted of all ThinPrep cases of atypical glandular cells of undetermined significance (AGCUS) or adenocarcinoma diagnosed between March 1998 and March 2000. Conventional smears collected between January 1996 and January 1998, before laboratory conversion to the ThinPrep system, comprised the control group. Histologic follow-up was obtained.

RESULTS. One hundred eighty-six (0.17%) of 112,058 ThinPrep Pap tests were interpreted as AGCUS/adenocarcinomas, compared with 77 (0.09%) of 83,464 conventional smears ($P < 0.001$). The overall sensitivity of a ThinPrep AGCUS/adenocarcinoma smear in detecting either cervical or endometrial adenocarcinoma was increased (72.0% vs. 41.5%; $P < 0.001$). The ThinPrep Pap test was more sensitive in detecting endometrial adenocarcinomas (65.2% vs. 38.6%; $P = 0.010$) and there was a trend for a higher sensitivity in detecting cervical adenocarcinomas (87.1% vs. 55.5%; $P = 0.108$).

CONCLUSION. The ThinPrep Pap test is a more sensitive method of detecting cervical and endometrial adenocarcinomas than the conventional Pap smear. ***Cancer (Cancer Cytopathol)* 2002;96:338–43.** © *2002 American Cancer Society.*

KEYWORDS: cervical adenocarcinoma, endometrial adenocarcinoma, ThinPrep, atypical glandular cells of undetermined significance (AGCUS).

The absolute frequency of cervical adenocarcinomas per 100,000 women is increasing relative to squamous cell carcinoma.[1] Current screening methods have been successful in detecting squamous disease, yet the recent statistics underscores the insufficiency of the conventionally prepared Papanicolaou (Pap) smear in detecting a significant number of adenocarcinoma precursors. Plaxe and Saltzstein[2] reported that the mean age of women with invasive cervical adenocarcinoma is 13 years older than women with in situ disease. Although the duration of disease progression suggests ample time for detection of precursor glandular lesions, the incidence of cervical adenocarcinomas continues to rise, indicating the need for improved screening methods.

Beginning in 1980, expanded cytologic criteria were introduced in an effort to improve the detection of precursor endocervical lesions.[3] These efforts have had limited success. The 1991 introduction of the Bethesda system resulted in classification of most of these lesions as atypical glandular cells of undetermined significance (AGCUS)-favor neoplastic.[4] The current usage of AGCUS correlates with a substantial

detection of cervical and endometrial adenocarcinomas.[5–10] However, greater than 50% of AGCUS Pap diagnoses actually represent a squamous lesion.[11] Intensive evaluation with colposcopy, cervical biopsy, endocervical curettage, and potentially endometrial biopsy has been proposed for all patients with an AGCUS smear to rule out the possibility of glandular neoplasia.[5,7–9]

Endometrial adenocarcinomas are the most common type of gynecologic malignancy, but the conventionally prepared Pap smear is not an effective screening method. Women are diagnosed routinely, despite having a preceding normal Pap smear.[12,13] The presence of excess blood and inflammation may obscure malignant cells, preventing accurate interpretation.[14]

The new liquid-based ThinPrep™ Pap test (Cytyc, Boxborough, MA) improves specimen adequacy and diagnostic yield.[15] Studies from different laboratories have documented increased detection of both low and high-grade squamous intraepithelial lesions with this test.[16–18] However, the performance of the ThinPrep Pap test in detecting glandular lesions is not as encouraging. Published reports describe greater difficulty in recognizing glandular lesions, decreased sensitivity to adenocarcinomas, or increased detection of cervical and endometrial glandular lesions.[19–22]

The purpose of this study was to compare the accuracy of the ThinPrep Pap test with the conventional Pap smear in detecting cervical and endometrial adenocarcinomas. In a retrospective cohort study of the stable patient population served by the Parkland Health and Hospital System, we report our experience following 100% laboratory conversion to the ThinPrep system.

MATERIALS AND METHODS

Patient Accession

The patients included in this study were from the high-risk inner-city population of Dallas County. Pap smears were obtained from the Parkland Health and Hospital System, including both hospital and community-based outpatient clinics. The hospital and its operated clinics are a closed system representing a stable patient population.

Subject Group

ThinPrep cervicovaginal smear diagnoses of adenocarcinoma or AGCUS over a 24-month period (March 1998–March 2000) after 100% conversion of the laboratory were identified retrospectively. The ThinPrep Pap smears were obtained by either the combination cytobrush/plastic spatula (Medscand USA, Hollywood, FL) or the broom-type sampling device (Papette; Wallach Surgical Devices, Millford, CT). The collected material was rinsed directly into PreservCyt® fixative solution (Cytyc), labeled with the appropriate patient information and sent to the cytology laboratory. A single ThinPrep slide was prepared from each patient sample on the ThinPrep 2000 automated slide processor (Cytyc) according to the manufacturer's instructions and stained with routine Pap stain.

Control Group

Conventional smears collected from January 1996 to January 1998, before laboratory conversion to the ThinPrep system, comprised the control group. These smears were derived from the same laboratory servicing the stable patient population of Dallas County. Samples were taken with a spatula/cytobrush combination, smeared on a single glass slide, and fixed with commercially prepared spray.

Pap Smear Reporting

The cytologic diagnoses of both the ThinPrep Pap subject group and the conventional smear control group were based on established criteria using The Bethesda system.[4] AGCUS smear diagnoses were subclassified when possible to indicate whether a reactive or neoplastic process was favored. Pap tests subclassified as undetermined did not have sufficient evidence for either a reactive or neoplastic process.

Histologic Follow-Up

A computerized search was conducted to obtain biopsy correlation for all cytologic diagnoses of adenocarcinoma/AGCUS for both subject and control groups. In addition, all biopsy-proven cases of cervical and endometrial adenocarcinomas were identified regardless of the preceding Pap smear diagnosis. Information was then retrieved for all Pap smears preceding the biopsy results for up to 3 years. All Pap smears preceding a confirmed cervical or endometrial adenocarcinoma that were not interpreted as adenocarcinoma/AGCUS were rescreened by a cytotechnologist and a cytopathologist.

Statistical Analysis

Two independent sample proportion tests were conducted to compare the accuracy of the ThinPrep Pap test with the conventionally prepared Pap smear in detecting cervical and endometrial adenocarcinomas.[23] Ninety-five percent confidence intervals (95% CIs) were calculated for the difference between these two proportion tests.[24] Alpha for all tests was 0.05.

RESULTS

One hundred eighty-six (0.17%) of 112,058 ThinPrep Pap tests in the subject group were interpreted as

TABLE 1
Subcategories of Pap Smears Interpreted as Adenocarcinoma

Subcategory	TP (%)	CS (%)	*P* value
Cervical	22 (42.3)	2 (11.8)	0.045
Endometrial	11 (21.1)	2 (11.8)	0.616
Not otherwise specified	19 (36.6)	13 (76.4)	0.010
Total	52	17	

Pap: Papanicolaou; TP: ThinPrep Pap test; CS: conventional smear.

TABLE 2
Subcategories of Pap Smears Interpreted as Atypical Glandular Cells of Undetermined Significance

Subcategory	TP (%)	CS (%)	*P* value
AGCUS-favor reactive	32 (23.8)	9 (15.0)	0.226
AGCUS-undetermined	35 (26.2)	30 (50.0)	0.002
AGCUS-favor neoplastic	46 (34.3)	12 (20.0)	0.065
AGCUS-endometrial origin	21 (15.7)	9 (15.0)	0.924
Total	134	60	

AGCUS: atypical glandular cells of undetermined significance; TP: ThinPrep Pap test; CS: conventional smear.

adenocarcinoma/AGCUS, compared with 77 (0.09%) of 83,464 conventional Pap smears in the control group ($P < 0.001$; 95% CI: −0.11–−0.04%). The prevalence of cervical and endometrial adenocarcinomas was 0.09% during the period of ThinPrep Pap collection, compared with 0.06% during the collection period of the conventional smears ($P = 0.053$).

The cytologic diagnosis of adenocarcinoma was identified in 52 ThinPrep and 17 conventional Pap smears (Table 1). ThinPrep screening resulted in the more frequent diagnosis of the cervical subcategory ($P = 0.045$; 95% CI, 0.6–60.5%) and fewer not-otherwise-specified diagnoses ($P = 0.010$; 95% CI, −71.1–−8.7%).

One hundred thirty-four ThinPrep and 60 conventional Pap smears reported as AGCUS were categorized further into AGCUS-favor reactive, AGCUS-undetermined, AGCUS-favor neoplastic, and AGCUS-endometrial origin (Table 2). The conventional Pap control group had proportionally more AGCUS-undetermined diagnoses ($P = 0.002$; 95% CI, −39.5–−8.3%).

Surgical pathology follow-up was available for 157 (84%) of 186 ThinPrep and 68 (88%) of 77 conventional smears (Table 3). The remaining 29 ThinPrep and nine conventional Pap cases had insufficient tissue for pathologic assessment or inadequate follow-up. The overall positive predictive value of an adenocarcinoma/AGCUS Pap smear in detecting cervical and endometrial adenocarcinomas was 45.9% in the ThinPrep subject group and 32.4% in the conventional Pap control group ($P = 0.082$). The ThinPrep Pap detected 27 (17.2%) cervical adenocarcinomas, compared with 5 (7.0%) in the control group ($P = 0.083$). A similar proportion of endometrial adenocarcinomas was detected in each group (ThinPrep: 28.7% vs. conventional Pap: 22.0%). The mean age for patients with cervical adenocarcinoma in situ (AIS)/adenocarcinoma and endometrial adenocarcinoma in the conventional Pap control group was 40.7 and 59.4 years, respectively. For ThinPrep, the age groups were 43.8 and 57.2 years, respectively, indicating a similar age incidence for the two groups. The introduction of the ThinPrep system resulted in fewer biopsy-proven miscellaneous squamous lesions (19.7% vs. 33.8%; $P = 0.036$; 95% CI, −27.3–−0.9%).

TABLE 3
Correlation of Adenocarcinoma/AGCUS Pap Smears with Histologic Diagnoses

Histologic diagnoses	TP (%)	CS (%)	*P* value
Adenocarcinoma	72 (45.9)	22 (32.4)	0.082
Cervical, in situ	13	2	
Cervical, invasive	14	3	
Endometrial	45	17	
Glandular atypia	4 (2.6)	3 (4.4)	0.748
Endocervical	3	3	
Endometrial hyperplasia	1	0	
Squamous lesions	31 (19.7)	23 (33.8)	0.036
Carcinoma	4	3	
High-grade SIL	11	11	
Low-grade SIL	16	9	
Benign condition	50 (31.8)	20 (29.4)	0.837
Total	157	68	

AGCUS: atypical glandular cells of undetermined significance; TP: ThinPrep Pap test; CS: conventional smear; SIL: squamous intraepithelial lesion.

A cytologic diagnosis of adenocarcinoma had a high positive predictive value, regardless of the collection method (ThinPrep: 87.5% vs. conventional smear: 77.8%; $P = 0.551$). The diagnosis of AGCUS-favor neoplastic had a higher positive predictive value than AGCUS-favor reactive ($P = 0.001$; 95% CI, 14.8–65.2%; Table 4). There was a trend for AGCUS-endometrial origin ThinPreps to have a higher prediction for underlying endometrial cancer compared with the conventional Pap control group ($P = 0.043$; 95% CI, 1.5–118.6%).

The ThinPrep subject group had 28 biopsy-proven cervical and endometrial adenocarcinoma cases in which the preceding smear was normal or had a diagnosis other than AGCUS; 31 such cases occurred in the conventional Pap control group (Table 5). The ThinPrep Pap test was a more sensitive method of detecting cervical and endometrial adenocarcinomas than

TABLE 4
Positive Predictive Value of AGCUS Pap Smear Subcategories in Detecting Cases of Cervical and Endometrial Adenocarcinoma

AGCUS subcategory	Cases/TP (%)	Cases/CS (%)
Favor reactive	0/24 (0)	0/6 (0)
Undetermined	5/30 (17)	3/27 (11)
Favor neoplastic	16/40 (40)	5/11 (45)
Endometrial origin	9/15 (60)	0/6 (0)
Total	134	60

AGCUS: atypical glandular cells of undetermined significance; TP: ThinPrep Pap test; CS: conventional smear.

TABLE 5
Cervical and Endometrial Adenocarcinomas with a Preceding Pap Diagnosis Other than Adenocarcinoma/AGCUS

Pap diagnosis	TP (n = 28)	CS (n = 31)
Normal	20	25
ASCUS	2	3
Low-grade SIL	1	1
High-grade SIL	5	2

AGCUS: atypical glandular cells of undetermined significance; TP: ThinPrep Pap test; CS: conventional smear; ASCUS: atypical squamous cells of undetermined significance; SIL: squamous intraepithelial lesion.

the conventional Pap smear (72.0% vs. 41.5%; $P < 0.001$; 95% CI, −48.1–−12.8%). The ThinPrep smear was more sensitive in detecting endometrial adenocarcinoma (65.2% vs. 38.6%; $P = 0.010$; 95% CI, 5.9–47.3%). The sensitivity of an adenocarcinoma/AGCUS ThinPrep smear in detecting cervical adenocarcinomas was 87.1%, compared with 55.5% in the control group ($P = 0.108$). The overall specificity ($P = 0.096$) and negative predictive value ($P = 0.163$) were not significantly different between he subject and control groups.

The overall false-negative rate was reduced in the ThinPrep subject group (28.0% vs. 58.5%; $P < 0.001$; 95% CI, −48.1–−12.8%). Twenty biopsy-proven cervical and endometrial adenocarcinoma cases had a preceding normal ThinPrep Pap smear; 25 preceding conventional smears in the control group were normal (Table 5). Of 20 normal ThinPrep Pap tests, 4 (20%) were screening errors that were reinterpreted as AGCUS/adenocarcinoma, compared with13 (52%) of 25 in the control group ($P = 0.059$). The remaining 16 ThinPrep and 12 conventional smears represented sampling errors.

DISCUSSION

The ThinPrep Pap test received approval in 1996 from the Food and Drug Administration. It enhances specimen adequacy, resulting in the cytologic diagnosis of significantly more cervical abnormalities than the conventional smear technique.[15] However, the efficacy of the ThinPrep Pap test in improving detection of glandular lesions is not well established.[8,16–18] The relative rarity of cytologic diagnoses of glandular abnormalities and the low prevalence of cervical and endometrial adenocarcinomas require a large number of smears to test the hypothesis that the ThinPrep Pap test is a more effective screening method.

Bai et al.[22] reported their experience comparing 82,252 ThinPrep with 82,754 conventional smears. Detection of biopsy-confirmed cervical glandular dysplasia/AIS was improved with the ThinPrep method (14.8% vs. 2.8%; $P < 0.05$).[22] In our study, there was a trend for increased detection of the ThinPrep Pap test in detecting invasive/in situ cervical adenocarcinoma (17.2% vs. 7.0%; $P = 0.083$). Further investigation of a larger sample size may be more conclusive in determining whether the ThinPrep Pap test is more effective in detecting cervical adenocarcinoma and its precursors.

Guidos and Selvaggi[25] reported an improved detection rate of endometrial adenocarcinoma ($P = 0.025$) among 29,589 ThinPrep smears, compared with 16,139 conventional Paps. We also observed an increased detection rate of endometrial adenocarcinomas using the ThinPrep system (65.2% vs. 38.6%; $P = 0.010$). AGCUS-endometrial ThinPrep smears were particularly predictive. Although endometrial adenocarcinomas are not considered lesions that are detected reliably using routine conventional Pap screening, the ThinPrep Pap test should be further evaluated prospectively.

In this retrospective cohort study, complete conversion to the ThinPrep system resulted in a higher incidence of AGCUS/adenocarcinoma smears ($P < 0.001$). This reflects both the higher prevalence at our medical center after 1998 and the increased sensitivity of the ThinPrep Pap test. In addition, cytologic interpretation was improved following laboratory conversion. The ThinPrep system resulted in fewer AGCUS-undetermined, fewer adenocarcinoma-not-otherwise-specified, and more adenocarcinoma-cervical origin Pap smears.

ThinPrep AGCUS-favor neoplastic smears were more predictive of a biopsy-confirmed adenocarcinoma compared with the AGCUS-favor reactive smears.[8] AGCUS-favor neoplastic smears frequently indicate an underlying adenocarcinoma, emphasizing the importance of aggressive clinical evaluation. The AGCUS-favor reactive subcategory rarely results in the histologic diagnosis of a significant glandular lesion.[5,8,26]

The false-negative rate of the ThinPrep Pap test was significantly lower in this study. When normal Pap smears preceding the diagnosis of endometrial and cervical adenocarcinomas were reinterpreted, there was a trend for reduced screening errors among the ThinPrep Pap tests. This finding is consistent with enhanced specimen adequacy of the ThinPrep system.[15] One possible explanation why ThinPrep smears reduce the false-negative rate of screening for glandular disease is elimination of obscuring elements such as blood and enhanced cytologic detail.

Looking at the potential biases in this study, it is unlikely that sampling devices would have contributed much to the increased detection of glandular disease. In our practice, the conventional smears were performed with a spatula cytobrush combination. In the ThinPrep Pap test, a combination of plastic spatula/cytobrush and broom-type devices were used. Therefore, the increased detection of glandular disease cannot be attributed to sampling devices alone.

Another potential bias may be due to enhanced detection of glandular lesions secondary to overall and improved training of the cytotechnologist and cytopathologist. The element of potential bias created by this fact can only be measured by completely rescreening all of the AGCUS/adenocarcinoma conventional smears collected between 1996 and 1998 to identify the improvement incurred with improved recognition. That was not the intent of this study.

It is unlikely that there would be a major increase in the incidence of adenocarcinoma of the uterine cervix and endometrium over this study period to introduce an element of bias related to increase incidence of disease. In addition to improved recognition of glandular abnormalities, the liquid-based Pap test provides opportunities for adjunctive additional testing such as the Digene Hybrid Capture II test for high-risk human papillomavirus types, which may be helpful in identifying underlying high-grade squamous and glandular lesions.[11] In addition, the residual specimen can be used to make cell block preparations by the inverted filter cell block[27] technique or other routine cell block methods, which may help to differentiate reactive glandular lesions from neoplastic lesions.

For all of the above reasons, we believe that the introduction of the ThinPrep Pap test in our laboratory has resulted in a significant improvement in the detection of glandular lesions. Our findings suggest that this system can facilitate a more directed approach to the evaluation and treatment of cervical and endometrial adenocarcinomas.

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