Evaluation of the ThinPrep Papanicolaou test in clinical practice: 6-month study of 16 541 cases with histological correlation in 220 cases

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Objective. To evaluate the liquid-based ThinPrep Papanicolaou test.
Design. Prospective comparison of the ThinPrep test with the conventional Papanicolaou test.
Setting. Cervical smear specimens sent to a private practice, Hong Kong.
Patients. A total of 16 541 ThinPrep test specimens and 7258 conventional Papanicolaou smears from Hong Kong women who had been screened for cervical cancer between mid-July 1998 and mid-January 1999.
Main outcome measures. Specimen adequacy, endocervical cell content, epithelial cell abnormalities, and micro-organisms present in both types of cervical smears; histological diagnosis of cervical biopsy specimens of women who had the ThinPrep test.
Results. Compared with the conventional Papanicolaou smear test, the ThinPrep test showed a reduction in the frequency of 'unsatisfactory' (0.56% versus 1.36%; P<0.01), 'satisfactory but limited' (1.67% versus 15.87%; P<0.01), and 'atypical squamous cells of undetermined significance' reports (1.72% versus 3.64%; P<0.01). The ThinPrep test was also more effective at detecting squamous intraepithelial lesions, showing a 58% increase for low-grade lesions (2.66% versus 1.68%; P<0.01) and 28% increase for high-grade lesions (1.71% versus 1.34%; P<0.01). The sensitivity and positive predictive value of the ThinPrep system were 97.5% and 94.2%, respectively. The liquid-based method yielded a higher percentage of samples that contained endocervical cells compared with conventional smear specimens (70.57% versus 51.23%; P<0.001).
Conclusions. The ThinPrep test has high a sensitivity and positive predictive value. The ThinPrep test gives higher-quality specimens and has a higher detection rate of squamous intraepithelial lesions than the conventional Papanicolaou smear test. The drawbacks of the liquid-based system, however, pertain to cost and the additional procedures and training needed.

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Key words: Cervical intraepithelial neoplasia; Cervix neoplasms; Cytological techniques; Laboratory techniques and procedures; Vaginal smears/methods

Introduction

The Papanicolaou (Pap) smear was introduced into clinical practice more than 50 years ago and has resulted in a significant reduction in cervical cancer mortality rates.[1] This achievement, however, has been partly overshadowed by recent concerns of the false-negative rate of the test, with reported estimates of up to 20%.[2,3] False negative results may be attributed to sampling errors (due to poor smear-taking techniques, design flaws of sampling devices, and inadequate smear preparation), as well as screening and interpretation errors. Recent studies indicate that sampling errors may account for approximately 67% to 90% of all false negative smear results.[2,3]

The recent exponential increase in the number of cases of litigation in the United States that have been attributed to false negative Pap test results[4] has led to the development of new methods to screen for cervical cancer. New innovations include computer-assisted screening devices (Papnet, AutoPap, and Autocyte Screen), liquid-based sample preparation

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devices (ThinPrep and Autocyte Prep), and screening process control devices (AcCell, PathFinder, and Cytosafe).[4] Liquid-based cytology systems, which are aimed at improving sample collection and preparation, have the most potential for reducing the false-negative rate. Computer-assisted screening devices and screening process control devices are helpful in reducing the frequency of the less common screening errors (such as cytotechnologists not noticing abnormal cells). These devices, however, cannot avert errors due to interpretation; these errors can be reduced only by adequate training of personnel, careful laboratory supervision, and stringent protocols.

The ThinPrep Pap test (Cytyc Corp., Boxborough [Mass], United States) was approved by the United States Food and Drug Administration in 1996 as a replacement for the conventional Pap test. This liquid-based sample-preparation system has been shown to be significantly more effective than the conventional Pap test.[5-14] The ThinPrep system was introduced into routine clinical practice at the Canossa Hospital laboratory in mid-July 1998. The objectives of this study were to determine the frequencies of abnormal smear results, sensitivity, and positive predictive value of the ThinPrep Pap test, and to compare this test with the conventional Pap test.

Materials and methods

All conventional Pap smear and ThinPrep samples that were submitted to our laboratory at the Canossa Hospital from mid-July 1998 to mid-January 1999 were included in this study. We visited all 171 practices who had previously submitted conventional Pap smear specimens and instructed them about the collection method of the new test. Approximately 82% (140/171) of the practices converted from using the conventional Pap smear test to using the ThinPrep Pap smear test during the 6-month study period. The remaining 18% of practices continued using the conventional Pap smear method, which uses the wooden Ayre spatula to collect the specimen. The decision to shift to the ThinPrep Pap test was left entirely to the individual practices. For the doctors who had changed to using the liquid-based ThinPrep system, we supplied the broom-like samplers (Cervex brushes; Rovers B.V., Oss, The Netherlands) to collect the specimen. Three doctors, however, preferred using the plastic Ayre spatula. Cells on the collection devices were rinsed directly into the vials of Preservcyt solution (Cytyc Corp., Boxborough [Mass], United States), which contained a methanol-based fixative, and the vials were submitted to our laboratory for processing (direct-to-vial protocol). No paired conventional smears were made with the ThinPrep specimens. Instead, the conventional smears in this study were sent by doctors in the early part of the study, before they converted to using the ThinPrep test (the CP-a group), as well as by doctors who continued using the conventional smear throughout the study period (the CP-b group).

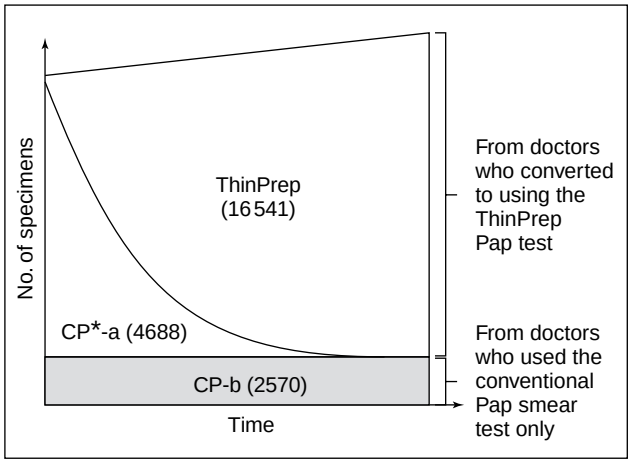
To test the null hypothesis that there was no difference in patient populations during the study period, the frequencies of abnormal smear results of samples sent by doctors who utilised the conventional Pap smear only and those who changed methods (ie the CP-a and CP-b samples) were compared by using the Chi squared test. All samples were subjected to primary screening by cytotechnologists and 100% rapid rescreening (non-blinded) by the sign-out pathologists as described in our previous study.[3] The same pool of cytotechnologists reported on specimens from both types of test. A modified Bethesda System was used to report the results; the data were coded for later analysis.[15] All ThinPrep cases that had follow-up biopsy samples were analysed as described in our previous study.[3] The Chi squared test (using the appropriate number of degrees of freedom) was used to compare category frequencies between the conventional Pap and ThinPrep groups.

Specimen adequacy was assessed using the Bethesda System guidelines[16] for conventional Pap smears. The 'satisfactory but limited' category was assigned to a slide when between 50% and 75% of the epithelial cells were obscured. Samples that lacked pertinent history and/or endocervical cells were not included in the 'satisfactory but limited' category. Smears in which more than 75% of the epithelial cells were obscured or if there were insufficient epithelial cells present were classified as 'unsatisfactory'. As there were no published criteria for assessing the ThinPrep slides, the Bethesda System guidelines were adapted. Because the ThinPrep slides tended to be more cellular at the periphery than at the centre of the slides, cells in poorly cellular specimens were more likely to be distributed as a ring at the periphery. ThinPrep slides were considered unsatisfactory if this cellular ring was less than 1.5 mm or almost the width of the microscopic field using the 10x objective, which corresponded to about 25% of the total area of the filter.

Results

Patient populations

The patient populations that were given the different tests are shown schematically in the Figure. During



CP* conventional Pap smear

Fig. Diagrammatic representation of the study population

the study period, the results of 7258 conventional Pap tests and 16 541 ThinPrep Pap tests were reported by our laboratory. The specimens had been submitted by 171 practices, 31 of which had submitted CP-b smears from 2570 patients. The remaining 4688 conventional Pap smears were CP-a samples (ie sent in by practices that later converted to using the ThinPrep Pap tests). There were no significant differences in the frequencies of abnormal or unsatisfactory smears (Table 1), or in the endocervical cell content of the CP-a and CP-b specimens, thus indicating that there were no differences between the two patient populations. The results of the CP-a and CP-b groups were combined for the comparison with the ThinPrep Pap test group.

Specimen adequacy

Of the 16541 ThinPrep specimens, 93 (0.56%) were unsatisfactory compared with 99 (1.36%) of the 7258 conventional Pap smears: a reduction of approximately 59% (Table 1; P<0.01). The main reason for the presence of unsatisfactory specimens for both the ThinPrep and conventional Pap tests was the insufficient epithelial cell content. The presence of obscuring inflammatory cells contributed to only two of the 93 unsatisfactory ThinPrep cases. The ThinPrep Pap test yielded a reduction of almost 90% of slides in the 'satisfactory but limited' category (Table 2). The most common reasons for classifying slides in this category of specimen were inflammation (10.94%) and scant cellularity (3.84%) for the conventional Pap test samples. The reasons for classifying the ThinPrep specimens in the 'satisfactory but limited' category were reversed in order of frequency (scant cellularity, 1.08%; inflammation, 0.68%) [Table 2]. Endocervical cells were present in 3718 (51.23%) of conventional Pap smears and in 11 673 (70.57%) of all ThinPrep specimens (P<0.001).

Epithelial cell abnormalities

The percentages of diagnostic categories of the two types of test showed statistically significant differences (Table 1). The percentage of reports of 'atypical squamous cells of undetermined significance' (ASCUS) from samples that were obtained by the conventional Pap test was 3.64%, whereas the corresponding figure for the ThinPrep Pap test specimens was 1.72% (P<0.01). The percentage of low- and high-grade squamous intraepithelial lesions (LSIL and HSIL) reports, however, were significantly higher for the ThinPrep Pap test (Table 1).

Follow-up histological examination results were available for 220 patients whose cervical samples had been prepared by the ThinPrep method. The correlation between the histological and cytological results is shown in Table 3. The overall absolute concordance rate for the series was 67.3% (148/220).

Table 1. Comparison of cytological reports from the conventional and ThinPrep smear tests

Report	CP-a*		CP-b†		Total (CP-a + CP-b)‡		ThinPrep		Change§	P value§
	No.	(%)	No.	(%)	No.	(%)	No.	(%)		
Unsatisfactory	66	1.41	33	1.28	99	1.36	93	0.56	-59%	<0.01
Negative	4282	91.34	2367	92.10	6649	91.62	15421	93.22	ns	ns
ASCUS[xx]	185	3.95	79	3.07	264	3.64	284	1.72	-53%	<0.01
AGUS[¶]	13	0.28	8	0.31	21	0.29	9	0.05	-	-
LSIL**	76	1.62	46	1.79	122	1.68	440	2.66	+58%	<0.01
HSIL[††]	62	1.32	35	1.36	97	1.34	282	1.71	+28%	<0.01
SCC[‡‡]	3	0.06	2	0.08	5	0.07	12	0.07	-	-
Adenocarcinoma	1	0.02	-	-	1	0.01	-	-	-	-
Total	2570		4688		7258		16541			

* CP-a conventional Papanicolaou test specimens from doctors who later changed to using the ThinPrep test
† CP-b specimens from doctors using only the conventional Papanicolaou test
‡ Results were pooled because they showed no statistically significant differences
§ Comparison of results from conventional smear specimens (CP-a + CP-b) with those of ThinPrep specimens
[xx] ASCUS atypical squamous cells of undetermined significance
[¶] AGUS atypical glandular cells of undetermined significance
** LSIL low-grade squamous intraepithelial lesion
[††] HSIL high-grade squamous intraepithelial lesion
[‡‡] SCC squamous cell carcinoma
ns not significant

Table 2. Quality of specimens from conventional Papanicolaou and ThinPrep tests

Feature	Satisfactory but limited				Unsatisfactory			
	CP*, n=7285		TP†, n=16 541		CP, n=7258		TP, n=16 541	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Inflammation	794	10.94	112	0.68	30	0.41	9	0.05
Blood	115	1.58	17	0.10	16	0.22	6	0.04
Atrophy	113	1.56	63	0.38	7	0.10	5	0.03
Cytolysis	34	0.47	8	0.05	4	0.06	-	-
Drying	27	0.37	-	-	2	0.03	-	-
Thick smear	49	0.68	-	-	1	0.01	-	-
Degeneration	5	0.07	-	-	-	-	-	-
Poor fixation	2	0.03	-	-	-	-	-	-
Scant cellularity	279	3.84	178	1.08	76	1.05	91	0.55
Total‡	1152	15.87§	277	1.67§	99	1.36xx	93	0.56xx

* CP conventional Papanicolaou smear specimen
† TP ThinPrep test specimen
‡ Some cases may have more than one feature; thus, the 'total' number of cases is not the same as the column total
§ Significantly different (P<0.01)
xx Significantly different (P<0.01)

When the ASCUS category was combined with that of LSIL and when the HSIL and carcinoma categories were combined, the concordance rates were 69.3% (61/88) for low-grade lesions and 81.7% (98/120) for high-grade lesions. There were insufficient follow-up biopsies for the conventional Pap smear group for meaningful histology-cytology correlation analysis in this study. All cases of ASCUS or above were considered to be 'positive' for the purpose of statistical analysis. Using this criterion and the histological diagnosis as the 'gold standard', the sensitivity and the positive predictive value of the ThinPrep Pap test were found to be 97.5% and 94.2%, respectively. The specificity and negative predictive value were not calculated in the study, because follow-up biopsy was not indicated in almost all cases that had a negative cytological report.

The ThinPrep test method yielded five false negative reports (ie normal cytology but a diagnosis of cervical intraepithelial neoplasia [CIN] from biopsy examination) during the short follow-up period (up to 9 months). In one of the false negative cases, carcinoma was present in the hysterectomy specimen but the ThinPrep cytological report had been negative and had stated the presence of scant atrophic cellular material. The patient in this case had presented with persistent vaginal bleeding, but the ectocervix was clinically normal and smooth. The hysterectomy specimen showed a large barrel-shaped carcinoma within the endocervical canal, which extended into the bladder and pelvic wall. On review, the ThinPrep specimen contained mostly proteinaceous debris and scant atrophic parabasal cells that were predominantly atrophic. The sample had originally been received during the initial trial period of the ThinPrep system and should have been reported as being unsatisfactory on retrospective review. The remaining four false negative cases were two cases of condylomata, one CIN I, and one case in which the biopsy specimen had changes that were suggestive of the presence of human papillomavirus (HPV). Review of the ThinPrep slides (and additional slides made from residual sample material) in these four cases, showed no cellular changes in three cases and non-specific reactive change in one case. It is likely that sampling error was the main cause of the false-negativity.

There were 12 false positive results from the ThinPrep test: three reports of ASCUS, six of LSIL,

Table 3. Cytohistological correlation of ThinPrep test results

Cytology	Histology					
	Normal	Atypia	CIN* I†	CIN II-III†	Carcinoma	Subtotal
Normal	7	0	4	0	1	**12**
ASCUS‡	3	3	16	1	1	**24**
LSIL§	6	2	40	16	0	**64**
HSILxx	3	2	17	94	0	**116**
Carcinoma	0	0	0	0	4	**4**
Subtotal	19	7	77	111	6	220

* CIN cervical intraepithelial lesion
† With or without human papillomavirus infection
‡ ASCUS atypical squamous cells of undetermined significance
§ LSIL low-grade squamous intraepithelial lesion
xx HSIL high-grade squamous intraepithelial lesion

and three of HSIL. One of the ASCUS cases was reported as 'favouring reactive' and the biopsy results were normal. The remaining two ASCUS cases showed evidence of immature squamous metaplasia on biopsy examination. Two of the six LSIL cases were subsequently shown to be positive for DNA of high-risk–type HPV, by subjecting the residual ThinPrep samples material to the Digene Hybrid Capture test (Digene Corp., Beltsville [Md], United States). Two of the three HSIL cases from the ThinPrep Pap test actually showed immature squamous metaplasia on histological examination; one of these two cases also showed associated endodysplasia. The third HSIL case showed typical cellular changes of CIN III when the ThinPrep slide was re-examined.

The presence of infection

Specific micro-organisms were identified in 654 (9.01%) of the conventional Pap smear samples and in 1386 (8.38%) of the ThinPrep specimens. There was no statistically significant difference in the overall rate of infection. The micro-organisms that were identified are shown in Table 4. There were statistically significant differences between the two test systems in the reporting of *Candida* species ($P<0.01$) and *Gardnerella vaginalis* ($P<0.01$). *Candida* spores were underrepresented on the ThinPrep slides, whereas the increased presence of *Gardnerella vaginalis* may be due to the washing and dilution effect of this liquid-based system, which makes the 'clue cells' more clearly visible in a relatively clean background.

Discussion

The ThinPrep Pap Test has been shown to be more effective than the conventional Pap test, and to have improved detection rates of squamous intraepithelial lesions of between 12% and 267%.[5-14] Early studies based on the split-sample protocol, in which the same patient acts as a control, showed significant improvements for the ThinPrep system in the detection of LSIL or more severe lesions.[5-10] The split-sample protocol is difficult to justify in routine clinical practice due to the substantially increased costs of performing two examinations and the shortage of qualified cytotechnologists. A direct-to-vial protocol is acceptable for routine clinical practice if it can be shown that this approach is just as effective as the split-sample protocol. It is, however, more difficult to conduct a direct-to-vial protocol study, as the same patient cannot be used as a control, because it is not possible to make a paired conventional smear after the specimen has been deposited into the vial. In this study there was no significant difference in the frequency of abnormal smears from the CP-a and CP-b samples. Hence, it is reasonable to assume that there were no significant differences between the ThinPrep and conventional Pap smear patient populations.

The concordance rates of the samples tested by the ThinPrep method were 67.3% overall, and 69.3% and 81.7% for low- and high-grade lesions, respectively. These results are higher than the previously published figures for the conventional Pap test of 51.2% overall, and 63.9% and 74.6% for low- and high-grade lesions, respectively.[3] This study also showed that the ThinPrep Pap test yielded 58% and 28% improvements in detecting LSIL and HSIL, respectively. The overall improvement for LSIL or more severe lesions was 43%, which is in the middle of the published range of improvements in the literature. The significant reduction in ASCUS reports reduced the number of equivocal cases arising from the ThinPrep test. Another advantage of the liquid-based cytology was the ability to perform HPV DNA assays on these equivocal cases. Patients whose samples show the presence of ASCUS and high-risk types of HPV may be followed up by colposcopy, while patients who are shown to be free of high-risk types of HPV may be followed up by repeating the smear test in 3 to 6 months.[17]

It has been assumed in previous studies that the improvements in results with the ThinPrep test have been due to the new method of collection, better preservation, slide preparation, and presentation of the

Table 4. Micro-organisms identified in cervical specimens

Organism	Conventional smears, n=7258		ThinPrep samples, n=16 541		P value
	No.	(%)	No.	(%)	
Candida species	593	8.17	1082	6.54	<0.01
Actinomyces species	3	0.04	15	0.09	-
Gardnerella vaginalis	19	0.26	236	1.43	<0.01
Herpesvirus	-	-	1	0.01	-
Trichomonads	39	0.54	52	0.31	-
Total	654	9.01	1386	8.38	ns

ns not significant

cells.[5-14] We believe that part of the reason for improved results in this study is the better collection of cell samples by using Cervex brushes. Almost all ThinPrep samples had been collected using Cervex brushes, while all conventional Pap test specimens had been taken using a wooden Ayre spatula. The fact that the Cervex brushes obtained better cell samples is supported by the higher percentage of specimens containing endocervical cells (70.57%) compared with the conventional Pap test (51.23%). Similar to the experience of Guidos and Selvaggi,[13] we have also seen a significant reduction in the number of 'satisfactory but limited' and 'unsatisfactory' reports. The former category is often problematic for clinicians, as they have to explain this problem to patients and conduct follow-up in such cases. The reduction in the number of unsatisfactory reports, and hence also the number of repeat tests needed, would clearly benefit both clinicians and patients.

Many published studies that demonstrate an increased detection rate of epithelial cell abnormalities with the ThinPrep system had not been supported by follow-up histology results.[5-14] It may be argued that the better results may simply be due to laboratory overreporting biases for the newer test (higher false-positive rates). The high positive predictive value (94.2%) and sensitivity (97.5%) calculated from biopsy results indicate that the better results obtained with the ThinPrep Pap test are not due to overreporting. These figures are slightly higher than previously published estimates for the conventional Pap test (positive predictive value, 93.5%; sensitivity, 91.7%).[3] Bolick and Hellman[12] reported a sensitivity of 95% with the ThinPrep method, compared to 85% with the conventional method.

Possible explanations for the discrepant histology-cytology results include sampling errors during smear-taking or biopsy at the time of colposcopy; the regression of HPV–induced changes during the interval between the smear-taking and the colposcopic biopsy; the removal of a small lesion (therapeutic smear); and technical limitations in the processing of biopsy specimens. Tissue blocks to be histologically examined are usually 2 to 3 mm thick; hence, it is possible that lesions smaller than 2 mm may be embedded deep in the block and not sectioned. In addition, there is some subjectivity and interobserver variability in the criteria that are used to interpret both biopsy material and Pap smears.[18-20]

One piece of misinformation about the ThinPrep Pap test is that small dysplastic cells are easily missed or filtered away during the preparation process. These cells are actually at least twice the size of the filter pores and are larger than polymorphonuclear leukocytes, which are readily visible on the ThinPrep slides. In addition, the detection of small metaplastic dysplastic cells in ThinPrep samples contributes to the increased detection rate of HSIL cases in this study. These cells are more difficult to identify on sub-optimally prepared conventional smears.

There are, however, some disadvantages of using the ThinPrep system: it costs more than the conventional test and the disposable plastic consumables are not recyclable. Indeed, practices who continued using the conventional smear test throughout the study period cited an increased cost (of HK$20 per test) as a reason for not changing. The introduction of the ThinPrep Pap test in our laboratory has resulted in an increase in costs, which are only partially passed on to the patients and thus substantially absorbed by the laboratory. The onus of producing a satisfactory slide for examination has shifted from the clinician to the laboratory. Consequently, the laboratory must perform a washing procedure for mucoid specimens and specimens that contain cellular debris, and a red blood cell–lysing procedure for heavily blood-stained specimens. The additional wash procedure (which is performed in about 15% of cases) further increases the cost of the test and increases the processing time for the laboratory. Occasionally, one must resort to making cell blocks to resolve diagnostically difficult cases,[21-23] the cost of which is many times the charge for the ThinPrep test. Thus, laboratories embarking on the use of liquid-based systems should be prepared to take on the additional workload, cost, and training. In addition, the laboratory must deal with a sufficient number of samples so as to encounter enough abnormal cases to maintain proficiency in recognising and interpreting abnormal epithelial cells in the liquid-based system.

This study shows that the ThinPrep Pap test method produces significantly better quality slides than does the conventional Pap test. The ThinPrep test is also better at detecting LSIL and HSIL, and has high positive predictive value, sensitivity, and histology-cytology concordance rates. However, the ThinPrep test, as with any screening test, has limitations with regard to sensitivity and specificity, and should not be considered as a diagnostic test.

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[Mass], United States. The company was not involved in the design or finance of the study, collection of the data, analysis of the results, or preparation of the manuscript.

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