The accuracy of Papanicolaou smear predictions: cytohistological correlation of 283 cases

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The Papanicolaou smear is a highly effective screening test for the detection of cervical neoplastic changes. The success of the test has resulted in unrealistic expectations of the accuracy of the test by both referring medical practitioners and the public. However, as with any pathological test, it has irreducible false negative and positive rates. This report is a comparison between interpretations based on cytological and histological tests and was undertaken to estimate the sensitivity of the Papanicolaou test as practised in Hong Kong. The overall absolute concordance rate for the study was 51.2%. The concordance rates within one diagnostic category were 63.9% and 74.6% for low- and high-grade squamous intraepithelial lesions, respectively. The overall sensitivity of the test was 91.7% with a positive predictive value of 93.5%. Ten percent of the error rate was attributed to laboratory error; the remainder was attributed to sampling error and poor smear preparation. Forty-five percent of cases of atypical squamous cells of undetermined significance showed evidence of cervical intraepithelial neoplasia on subsequent biopsy. Follow-up biopsies of low-grade squamous intraepithelial lesions also showed as many lesions from cervical intraepithelial neoplasia grade I as from grades II and III. These findings suggest that colposcopies and biopsies should be performed as soon as possible rather than to repeat the smears in 3 to 6 months. The results of the study may provide guidelines for formulating follow-up recommendations.

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Key words: Cervical intraepithelial neoplasia; Cervix neoplasms; Diagnostic error; Predictive value of tests; Sensitivity and specificity

Introduction

The use of the Papanicolaou (Pap) smear has resulted in a dramatic decline in the mortality and morbidity rates of cervical cancer in many western countries. A similar decline in mortality rate has also been seen in Hong Kong.[1] The success of the Pap test has resulted in unrealistic community expectations,[2] with a consequent rise in litigation when false negative cases arise. It is important for primary physicians to be aware that, as with any pathological test, there are recognisable false-positive and false-negative rates for the Pap test. We have undertaken a study to estimate the accuracy of the Pap test as practised in a private laboratory in Hong Kong, to provide primary physicians with some indication as to the accuracy of the test. The accuracy of any test can be expressed statistically in terms of sensitivity and specificity. Traditionally, the 'gold standard' for assessing the performance of Pap smear predictions has been the histology of cervical biopsies taken shortly after the Pap smear has been performed. Although it is acknowledged that histology suffers similar, but to a lesser extent, problems with intra- and inter-observer reproducibility[3,4] and sampling error, it nevertheless provides a reasonable parameter to gauge the performance of the Pap test. Similar cytohistological studies have been published for western countries.[5-8] The results of this study may provide some guidelines for formulating follow-up recommendations for women with abnormalities detected by screening.

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Materials and methods

All Pap smears in our laboratory were subjected to primary screening by a qualified cytotechnologist with no less than 5 years' screening experience, followed by rapid rescreening by a supervising pathologist before sign-out. We used both the Bethesda system and the equivalent cervical intraepithelial neoplasia (CIN) grading in our reports. All cases of Pap smears that were reported as low-grade squamous intraepithelial lesions (SIL) or higher between January and December

1996 were retrieved from the files. Records were easy to retrieve as we used a standardised reporting protocol with automated optical mark sensing, as previously reported.[9] A search of the histological records from January 1996 to March 1997 was conducted to look for corresponding follow-up biopsies for each patient with an abnormal Pap smear report. Conversely, all biopsy cases containing the word string 'cervi' in the diagnostic field were retrieved from the histological database and checked for a corresponding Pap smear from the preceding 6 months. Matching cases of Pap smears and biopsies were tabulated. As there were only a few cases of glandular lesion, low-grade endodysplasia and low-grade SIL were combined as low-grade epithelial lesions (LGEL) for the purpose of statistical analysis. Similarly, high-grade SIL and high-grade endodysplasia were combined as high-grade epithelial lesions (HGEL). Pure human papillomavirus (HPV) lesions were classified as low-grade SIL. Cases showing a deviation of one diagnostic grade between the cytological and histological reports were classified as minor over-reporting if Pap smears were reported as one diagnostic grade higher than the corresponding histological report. Similarly, cases were classified as minor under-reporting if Pap smears were reported as one diagnostic grade lower than the histological report. Cases were classified as major over-reporting if the Pap smear was reported as high-grade with negative histology on follow-up biopsy, and major under-reporting if the Pap smear was reported as negative with subsequent high-grade epithelial lesions on histology. All Pap smears and histological slides showing major discrepancies were retrieved and reviewed to determine the reasons (if any) for the discrepancies.

Results

A total of 34 570 cases of Pap smears were reported in 1996. The number and proportions of various diagnostic categories are shown in Table 1. The percentages of 'positive' categories are much higher than reported in routine screening in Hong Kong[10] and this is possibly explained by the high proportion of specialist gynaecologists' referrals in our series. Seven hundred and fifty-three histology reports of cervical biopsies and hysterectomy specimens for cervical pathology were retrieved from the histology files and the diagnostic categories are presented in Table 2. The higher percentage of biopsies for higher-grade lesions is consistent with the current recommendations for performing colposcopy and biopsy. Adenocarcinoma in our series of predominantly Chinese patients comprises about 17% of all carcinoma cases mirroring the increased relative incidence of this carcinoma, as reported in western communities.[11-14]

Table 1. Diagnostic categories of Pap reports for 1996

	No. of cases (%)
Unsatisfactory	180 (0.52)
No malignant cells seen	26 895 (77.79)
Reactive cellular changes	6 294 (18.21)
ASCUS*	792 (2.29)
Low-grade epithelial lesions	225 (0.65)
High-grade epithelial lesions	158 (0.46)
Carcinoma	26 (0.08)
Total	**34 570**

*ASCUS atypical squamous cells of undetermined significance

Table 2. Diagnostic categories of histological specimens of cervix for 1996

	No. of cases (%)
Normal or reactive changes	111 (14.7)
Mild basal cell atypia/atypical metaplasia	84 (11.2)
CIN* I ± HPV† infection	186 (24.7)
CIN II-III	327 (43.4)
Adenocarcinoma in situ	5 (0.7)
Squamous cell carcinoma	33 (4.4)
Adenocarcinoma	7 (0.9)
Total	**753**

*CIN cervical intraepithelial neoplasia
†HPV human papillomavirus

We identified 283 matching cases between the cytological and histological records. The correlation between the histology and cytology is shown in Table 3. The biopsy material represented 0.066% of all cases reported as negative or showing reactive cellular changes, 8% of atypical squamous cells of undetermined significance (ASCUS), 36% of low-grade cases, 65% of high-grade cases, and 37% of carcinoma cases. The lower rate of biopsies for carcinoma cases was because many of these patients were referred or presented themselves to public hospitals for further management. Of the 26 cases of carcinoma reported from the Pap smears, no follow-up information was available to the primary physicians in 16 cases, suggesting there was poor communication between public hospitals and primary physicians in private practice.

The absolute concordance rate for the study was 52%. When ASCUS was combined with low-grade

Table 3. Cytohistological correlation of 283 cases

	Histology					
	Neg/RCC*	Atypia	CIN† I	CIN II-III	CA‡	**Total**
Cytology						
Neg/RCC		1	11	10		**22**
ASCUS§	6	30	19	10	1	**66**
LGEL‖	3	8	37	32	1	**81**
HGEL¶	8	2	19	72	3	**104**
CA				4	6	**10**
Total	**17**	**41**	**86**	**128**	**11**	**283**

*Neg/RCC negative or reactive cellular change
†CIN cervical intraepithelial neoplasia
‡CA carcinoma
§ASCUS atypical squamous cells of undetermined significance
‖LGEL low-grade epithelial lesion
¶HGEL high-grade epithelial lesion

cases and carcinoma was combined with high-grade cases, the concordance rate was 63.9% (94/147) for LGEL and 74.6% (85/114) for HGEL. The 18 cases showing more than one diagnostic grade (major discrepancies) comprised eight cases of over-reporting and 10 cases of under-reporting. Review of the eight cases of over reporting showed definite high-grade SIL changes in five cases and three cases were downgraded to low-grade SIL. The biopsy material in the five cases of definite high-grade SIL on Pap smears showed chronic inflammation, decidualised endocervical polyp, metaplasia, endocervical tissue only (endocervical curettage specimen), and normal squamous mucosa. The case with normal squamous mucosa was from a 70-year-old woman who had previously had hysterectomy for carcinoma of the cervix. Repeated colposcopies were normal and complete stripping of the vault mucosa showed atrophic epithelium. Repeat Pap smears 3 and 4 months later were again reported as high-grade SIL. The patient was then treated with local oestrogen cream prior to her latest smear at 6 months, which showed a normal smear with oestrogen effect. The cause of false positive reporting in this case was attributed to atrophy. The remaining four high-grade and three low-grade cases were possibly due to sampling error and required longer follow-up.

Review of the 10 cases of under-reporting showed one false negative case, three cases which were reported as unsatisfactory or suboptimal due to air drying, and six cases in which no abnormal cells were seen. The single true false-negative contained very few abnormal CIN II cells. The abnormal cell nuclei were difficult to assess due to partial air drying. Thus, laboratory false negativity contributed to only 10% (1/10) of the overall false negative cases. The causes of the false negative cases were presumed to be due to sampling error, poor smear taking, and slide preparation (nine of 10 cases).

The calculation of the sensitivity and predictive value of a test depends on the definition of the 'disease state' that separates 'positive' from 'negative'. If a report of ASCUS and above is considered as positive for the purpose of statistical analyses, the overall sensitivity of this study was 91.7% (244/266) or 94.8% (244/257) if the nine false negative cases due to sampling and poor preparation are excluded. The overall false negative rate of 8.3% is comparable with the average major discrepancy rate of 5% in an Interlaboratory Comparison Program.[15] The positive predictive value was 93% (244/261).

Discussion

A common misconception of the public and many primary physicians is that the Pap smear is an accurate diagnostic test. It has been demonstrated in this report and many others, that the Pap smear is an imperfect screening test. The overall false-negative rate of 8.3% for Pap smear reported in this study is comparable with those reported in the literature, which are at least 5%, even in the best laboratories.[15,16] It is, however, difficult to make direct comparison of the error rates for the Pap smear in the literature as the values differ depending on the definition of 'disease state.' A major component of the false-negative rate appears to be sampling and preparation artifacts. The laboratory false-negative rate in this series contributed just 10% of the overall false negative cases. This is despite carrying out 100% rapid rescreening of every smear. The only way to reduce the false-negative rate for an individual patient is to repeat smears at regular intervals. It is

estimated that the error rate can be reduced to a negligible level with three normal consecutive annual smears. However it must be emphasised that patients with unexplained symptoms must be followed up, despite negative Pap smear reports. This point is well illustrated in this study where 21 biopsies from 22 cases reported as normal in the Pap smears showed CIN. These biopsies were performed because of clinical suspicion or persisting unexplained symptoms.

This study is valuable as it gives local referring practitioners an idea of the accuracy of the Pap test in the local environment. The results of this study also suggest some guidelines for the follow-up of abnormal Pap smears. Current practice in Hong Kong is to recommend a follow-up Pap smear at 6 months for ASCUS and at 3 months for low-grade SIL. The follow-up for smears reported as ASCUS should, in our view, be more aggressive, as 30 of the 66 (45.5%) cases of ASCUS in our series were graded at CIN I or higher when subjected to biopsy, and included one carcinoma. There is an increasing appreciation of the need to separate cases of ASCUS into those without qualifier and those favouring SIL. High proportions of cases labelled 'ASCUS favours SIL' have been shown to contain SIL on biopsy.[17] Similarly, one can argue for a more active follow-up of low-grade lesions, since nearly as many CIN II-III as CIN I cases were diagnosed on follow-up biopsies of low-grade lesions.[18]

When a discrepancy occurs in a study of cytohistological correlation, it is usual to assume that the discrepancy is due to error in the Pap smear reading. However, as demonstrated in this report, a review of the so-called false positive cases showed definite cytological abnormalities in the Pap smears. The converse is also true, as it is not uncommon for a Pap smear taken at the time of colposcopic biopsies to be negative and the biopsy to show CIN II-III. These phenomena are probably due to sampling errors. Instead of assuming that the Pap test is inaccurate when there is a discrepancy, it is perhaps more appropriate to take the test with the higher degree of abnormality as the 'correct' result. This can be extended to incorporate the colposcopic and clinical findings and so use the four modalities (quadruple screening tests) together in determining the management of each individual patient, much like the triple (clinical, imaging, and fine needle aspiration cytology) diagnostic criteria for the detection of breast carcinoma.

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