Comparison of conventional Papanicolaou smear and SurePath® liquid-based cytology in the Copenhagen population screening programme for cervical cancer

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Objective: To compare diagnostic performance of conventional Papanicolaou smear with SurePath® liquid-based cytology in a population screening programme.

Methods: A retrospective comparison was performed on data from two 18-month periods of the screening programme for cervical cancer in the municipality of Copenhagen with conventional Papanicolaou technique ($n = 82\ 116$) and liquid-based cytology ($n = 84\ 414$).

Results: After the conversion to liquid-based cytology the percentage of unsatisfactory samples decreased from 2.3% to 0.3% ($P < 0.001$), whereas the number of normal cervical samples lacking an endocervical component increased from 8.5% to 8.9% ($P < 0.005$). The percentage of samples with atypical cells and cells suspicious for malignancy increased from 3% to 4.2% ($P < 0.001$) and from 1.9% to 2.4% ($P < 0.001$), respectively. The subsequent histological follow-up showed normal findings decreased from 70.5% to 68.9% and from 28.0% to 26.1%, respectively. However, in relation to the entire screening populations, there was an increase of normal findings from 2.12% to 2.89% after primary atypical diagnosis and from 0.53% to 0.62% after diagnosis of suspicious cells after conversion to the liquid-based technique.

Conclusions: This study showed the number of unsatisfactory samples to be significantly reduced with the liquid-based technique. The data suggest that there is an increased detection rate of cervical precancerous lesions with liquid-based cytology, but the number of false positive tests is still high. The specificity of the two tests seems similar, but this cannot be ascertained exactly, because of the fact that follow-up of negative cases is unavailable.

Keywords: conventional cervical cytology, liquid based cytology, screening programme, sensitivity, specificity, inadequate samples

Introduction

With the aim of detecting cancerous and precancerous lesions of the cervix, thereby reducing the mortality of cervical cancer, a population-based screening programme was introduced in Denmark in the mid 1960s. The Danish National Board of Health recommended that all women between 23 and 59 years of age should be offered a cervical smear free of charge every third year. Since 1996, the administration of the screening programme in the municipality of Copenhagen, together with the cytological evaluation, has been centred at the Department of Pathology at Hvidovre Hospital. The department evaluates approximately 60 000 cervical samples each year.

The conventional cervical smear technique, as developed by George Papanicolaou, where cells from the endo- and ectocervix are transferred to a slide, prepared and evaluated, has been used in screening for cervical cancer since the 1940s.[1] The test has been regarded as the most successful screening tool for cancer in the history of medicine.[2] Several major studies have concluded that mortality rates from cervical cancer have decreased following the initiation of regular screening programmes.[3] In spite of this, it is widely agreed that the

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technique has its limitations, especially a significant false-negative rate. Gay *et al.* reported a false-negative rate of 20%, and in concurrence with other investigators, found preparation and sampling errors to account for the greater part.[4] A high number of smears are limited by obscuring blood, inflammation and mucus or show inadequate cellularity.[5–7] Investigators have observed that as much as 80% of cellular material remains in the collecting device and is discarded after conventional smears are prepared.[8] Such unsatisfactory smears require retesting. This increases the costs and workload of the departments of pathology and gynaecology and entails more anxiety for the women.

Liquid-based cytology (LBC) for screening for cervical malignancy was developed in the 1960s and 1970s, and has been acknowledged as an alternative to conventional Papanicolaou smear (CPS).[9] The first liquid-based screening method was approved by the American Food and Drug Administration in 1996.[5,10] Investigators supporting LBC claim that there are fewer unsatisfactory samples, that more of the original cells are represented in the final specimen and that it is faster and more efficient.[5–7] Several clinical trials suggest that interpretation of LBC preparations is more accurate and is associated with fewer screening errors than interpretation of CPS.[11] Furthermore, the residual material of the LBC samples can be used for other diagnostic analysis, as for example HPV testing.[5,7]

At the Department of Pathology, Hvidovre Hospital, we converted our screening method from CPS to LBC in May 2002. The conversion was carried out from one day to the other after a trial period of 3 months involving a pilot group of general practitioners and gynaecologists. Prior to the conversion to LBC, all involved pathologists and cytotechnicians received advanced courses in LBC. Several investigators have tried to compare the effectiveness of liquid-based cytology with conventional Papanicolaou methods, but to our knowledge, only a few studies have been carried out with a population as large as ours. The purpose of this study was to compare diagnostic results of liquid-based cytology with historical data of conventional smear from an identical patient population. In doing so, we hope to be able to assess the performance of LBC compared with CPS, when it comes to specimen adequacy and diagnostic efficacy.

Methods

A retrospective comparison was performed on data from two 18-month periods of the population screening programme for cervical cancer in the Municipality of Copenhagen. In the first period, 1 January 2000 to 30 June 2001 (hereafter named period 1), CPS was the method in use. In the second period, 1 January 2003 to 30 June 2004 (hereafter named period 2), LBC was the screening technique in the department. In period 1 the department received 82 116 smears, whereas we received 84 414 cervical samples in period 2.

In 2002, LBC was implemented in the department, and our cytopathologists and cytotechnicians were being trained to evaluate the new smears, so data from this year have not been included in the study. In Denmark general practitioners collect most cervical smears. A minor part is performed by specialists in gynaecology, either in hospitals or in private practice. There was no difference in this procedure in the two study periods.

Formerly, our department used a classification different from the Bethesda classification. Our diagnosis 'atypical cells' covers the diagnoses atypical squamous cells of uncertain significance (ASC-US) and low grade squamous intraepithelial lesions (LSIL) in the Bethesda classification. Our diagnosis 'cells suspicious for malignancy' covers the diagnoses atypical squamous cells of high grade (ASC-H), high grade squamous intraepithelial lesions (HSIL), adenocarcinoma *in situ*, squamous carcinoma and adenocarcinoma in the Bethesda system. The reason for this classification was to simplify and improve communication with the clinicians.

All cervical samples with the diagnosis 'atypical cells', 'cells suspicious for malignancy' and 'unsatisfactory for evaluation' are supplied with recommendations for follow-up. After the diagnosis of 'unsatisfactory for evaluation' or 'atypical cells', new cytological sampling is performed after 3 months. If this cytological sample is normal, the woman is returned to the screening programme without further testing. In cases of persistent 'atypical cells' and in all cases of 'cells suspicious for malignancy', the woman is referred to colposcopy, cervical abrasion and biopsy. In cases with normal histological follow-up after cytological diagnosis of 'cells suspicious for malignancy', new cytological sampling is performed after 3 months. If this test is normal, the woman is likewise returned to the screening programme.

Our screening setup entails some artificial 'false-positive cases', i.e. cases with regression of the lesion before follow-up or true lesion missed on follow-up colposcopy and biopsy. This is, however, similar in both study periods. In cases with no relevant follow-up, the physician responsible receives a reminder. Thus, our department has a follow-up rate of close to 100% of

abnormal screening samples. Our recommendations have been the same in both study periods, and the demographics of the women are likewise similar.

Period 1 – Conventional Papanicolaou Smear

Since 1999, the Department of Pathology at Hvidovre Hospital has been using the FocalPoint® automated analyzer (TriPath Imaging®, Inc., Burlington, NC, USA) for primary screening of the smears from the population screening programme. In the time period of CPS, the FocalPoint® analyzer was set for a cut-off point of 50% for normal smears. Ten per cent of these samples underwent rapid rescreening as quality control, and the rest (40%) were signed out with no further review. The remaining smears were all fully screened by 15 fulltime cytotechnicians. The smears were then either signed out as normal, or forwarded to one of the three cytopathologists in the department for final diagnosis.

Rapid rescreening is performed over 30 seconds in a stepwise fashion in our institution, whilst full screening is performed in an organized vertical and overlapping fashion. The gynaecological smear sampling was performed by general practitioners and gynaecologists with the use of a wooden Ayre spatula for ectocervix and the Cytobrush® Plus (Medscand Medical AB, Malmø, Sweden) for the endocervix. Slides were immediately fixed in 95% ethanol and stained by the Papanicolaou method.

Period 2 – Liquid based cytology

After the conversion to LBC in our department, rapid rescreening is conducted as quality control on all of the 50% of cervical samples that the FocalPoint® analyzer evaluates as normal. The remaining samples are treated as previously described. To make the two study periods comparable, the positive samples found by the rescreening in period 2 have been excluded. The staff concerned with the cervical population screening programme is now reduced to 11 full-time cytotechnicians, but still includes three cytopathologists. The change in workload reflected by the change in setting of the FocalPoint® analyzer has been extracted from the figures.

For processing the liquid-based cervical samples, our department has chosen to use the SurePath® slide preparation technique (TriPath Imaging®). The technique is described in more detail in earlier studies.[12]

The cytological samples are now collected with the Cervex-Brush® system (Rovers Medical Devices, B.V., Oss, the Netherlands), where the brush heads are placed in vials containing buffered alcohol preservative solution and sent to the laboratory for processing and evaluation.

Statistical analysis has been carried out with McNemar chi-square test for testing the zero hypothesis that there is no difference between conventional Papanicolau smear technique and liquid-based cytology, when it comes to quality and diagnosis of precancerous and cancerous lesions of the cervix. The statistical significance of differences between categories was assessed using chi-square test with 1 d.f. and results with $P < 0.05$ were considered statistically significant.

Results

The number and distribution of cytological diagnoses in the two periods are shown in Table 1. The total number of tests was 82 116 and 84 414 in period 1 and 2, respectively. As shown, the percentages of cervical samples diagnosed as atypical cells and cells suspicious for malignancy increased by 40% and 23.3% after the conversion to LBC. The increase is statistically significant ($P < 0.001$ for both categories). The percentage of unsatisfactory samples decreased

Table 1. The number and distribution of cytological diagnoses in period 1 and period 2

	Total number of samples, *n*	Normal cells, *n* (%)	Normal cells, no endocervical cells, *n* (%)	Atypical cells*, *n* (%)	Cells suspicious for malignancy*, *n* (%)	Unsatisfactory for evaluation, *n* (%)
Period 1	82 116	69 224 (84.3)	6966 (8.5)	2468 (3.0)	1544 (1.9)	1914 (2.3)
Period 2	84 414	71 040 (84.2)	7540 (8.9)	3539 (4.2)	2003 (2.4)	292 (0.3)
Change in %		NS (−0.1)	$P < 0.005$ (4.7)	$P < 0.001$ (40)	$P < 0.001$ (23.3)	$P < 0.001$ (87)

*The diagnosis 'atypical cells' covers the diagnoses ASC-US (atypical squamous cells of uncertain significance) and LSIL (low grade squamous intraepithelial lesions) in the Bethesda classification. The diagnosis 'cells suspicious for malignancy' covers the diagnoses ASC-H (atypical squamous cells of high grade), HSIL (high grade squamous intraepithelial lesions), adenocarcinoma *in situ* and squamous and adenocarcinoma in the Bethesda classification.

from 2.3% in the period of CPS to 0.3% after the introduction of the liquid-based technique ($P < 0.001$), whilst the number of cervical samples containing normal cells, but lacking an endocervical component increased from 8.5% to 8.9% ($P < 0.005$).

Table 2 shows follow-up diagnoses in period 1 and 2 in relation to the entire study populations. In period 1, there was a total number of 2468 cervical specimens with the diagnosis of 'atypical cells' and 1544 specimens had a diagnosis of 'cells suspicious for malignancy'. The numbers for period 2 were 3539 and 2003, respectively.

In relation to the entire population, there was an increase from 2.12% to 2.89% of false-positive diagnoses of atypical cells and from 0.53% to 0.62% of false-positive diagnoses of cells suspicious for malignancy after conversion to LBC. On the other hand, the table shows that in this analysis there were also higher percentages of cases in both the 'mild, moderate and severe dysplasia/CIS' group with LBC than with CPS.

Nearly all of the patients receiving a cytological diagnosis of 'cells suspicious for malignancy' had a biopsy specimen/cone biopsy performed as recommended. The positive predictive value (PPV) for this diagnostic group defined as the probability of having moderate dysplasia or worse, is 0.65 and 0.63 in the period of CPS and LBC, respectively. Because of the classification formerly used in our department, it has not been possible to subdivide this diagnostic group into ASC-H and HSIL.

According to Koss, one of the best methods of quality control is the comparison of cytology with corresponding histology.[13] Table 3 shows the correlation between the cytological diagnoses and the subsequent follow-up. Furthermore, it shows the distribution of follow-up diagnoses in the two study periods. The percentage of normal tests, i.e. false-positive cases found after biopsy or new cytological evaluation due to the finding of atypical cells or cells suspicious for malignancy, decreased after the introduction of LBC from 70.5% to 68.9% and from 28.0% to 26.1%, respectively. There was an increase in the percentage of follow-up diagnoses in the categories of 'mild' and 'moderate dysplasia', but a decrease in the categories of 'severe dysplasia/CIS' and 'carcinoma' after cytological evaluation of atypical cells with the liquid-based technique. Likewise, there was an increase in the percentage of follow-up diagnoses in the category of 'mild dysplasia', but a decrease in the categories of 'moderate dysplasia' and 'carcinoma' after cytological evaluation of cells suspicious for malignancy with LBC. There was no difference in the percentage of diagnoses in the category 'severe dysplasia/CIS' after cytological evaluation of cells suspicious for malignancy in the two study periods.

The category of 'normal test' in the tables is composed of both normal cytological samples taken as control after the primary diagnosis of atypical cells and of normal histological samples (biopsy specimen/cone biopsy) taken as control after primary diagnosis

Table 2. Follow-up after cytological diagnosis of atypical cells and cells suspicious for malignancy in period 1 and period 2 in relation to entire study populations

	Atypical cells*		Cells suspicious for malignancy*	
Diagnosis after follow up	Period 1	Period 2	Period 1	Period 2
Normal test[†,‡]	1739 (2.12)	2437 (2.89)	432 (0.53)	523 (0.62)
Mild dysplasia	236 (0.29)	456 (0.54)	113 (0.14)	228 (0.27)
Moderate dysplasia	134 (0.16)	220 (0.26)	169 (0.21)	179 (0.21)
Severe dysplasia and CIS	349 (0.43)	421 (0.50)	789 (0.96)	1023 (1.21)
Carcinoma	10 (0.01)	5 (0.006)	41 (0.05)	50 (0.06)
Total	2468 (3.0)	3539 (4.2)	1544 (1.9)	2003 (2.4)

Values are given as *n* (%). Total no. of tests: period 1 = 82 116; period 2 = 84 414.
*The diagnosis 'atypical cells' covers the diagnoses ASC-US and LSIL in the Bethesda classification. The diagnosis 'cells suspicious for malignancy' covers the diagnoses ASC-H, HSIL, adenocarcinoma *in situ* and squamous and adenocarcinoma in the Bethesda classification.
[†]Cytological false-positive diagnoses.
[‡]The primary diagnosis 'atypical cells' is followed by a new cytological test within 3 months. When there are normal cells in this control, it is included in the category of normal test. The primary diagnosis 'cells suspicious for malignancy' is followed by histological verification directly, i.e. biopsy or cone biopsy.

Table 3. Distribution of follow-up diagnoses after a diagnosis of atypical cells and cells suspicious for malignancy in Period 1 and 2

	Atypical cells*		Cells suspicious for malignancy*	
Diagnosis after follow-up	Period 1 (%)	Period 2 (%)	Period 1 (%)	Period 2 (%)
Normal test †,‡	70.5	68.9	28.0	26.1
Mild dysplasia	9.6	12.9	7.3	11.4
Moderate dysplasia	5.4	6.2	10.9	8.9
Severe dysplasia and CIS	14.1	11.9	51.1	51.1
Carcinoma	0.4	0.1	2.7	2.5
	100	100	100	100

Total atypical tests: period 1, $n = 2468$; period 2, $n = 3539$. Total tests suspicious for malignancy: period 1, $n = 1544$; period 2, $n = 2003$.
*The diagnosis 'atypical cells' covers the diagnoses ASC-US and LSIL in the Bethesda classification. The diagnosis 'cells suspicious for malignancy' covers the diagnoses ASC-H, HSIL, adenocarcinoma *in situ* and squamous and adenocarcinoma in the Bethesda classification.
†Cytological false-positive diagnoses.
‡The primary diagnosis 'atypical cells' is followed by a new sample within 3 months. When there are normal cells in this sample, it is included in the category of normal test. The primary diagnosis 'cells suspicious for malignancy' is followed by histological verification directly, i.e. biopsy or cone biopsy.

of 'cells suspicious for malignancy'. All three tables include explanatory notes making comparison with the Bethesda classification possible.

Discussion

Unlike many earlier studies, where liquid-based samples have been made from residual material from conventional smears, our LBC samples are made direct to vial. In our opinion this gives a better picture of the adequacy and diagnostic efficacy of liquid-based cytology. In the period of CPS, the FocalPoint® analyzer was set for a cut-off point of 50% for normal smears. This was carried out because a pilot study performed before the introduction of the analyzer showed no difference in the observed results between screening by cytotechnicians and screening by FocalPoint® set at 50%. This also solved the problems with the lack of cytotechnicians.

There have been divergent opinions about liquid-based cytology. The Australian Health Technology Advisory Committee Report and the Canadian Coordinating Office for Health Technology Assessment concluded that LBC would increase the detection of cervical abnormalities and decrease the number of unsatisfactory samples, but decided that the relative improvement in sensitivity was not sufficient to mandate universal introduction of the technique.[14,15] Moreover, the relative costs per additional cancer prevented were considered too high and would divert resources from important parts of the screening programme.[14,15] The New Zealand Health Technology Report concluded that test sensitivity and specificity could not be reliably determined, and that economic models therefore could not be evaluated.[16] The author also warned that an increase in test sensitivity could decrease test specificity and thereby increase the number of false-positive samples.[16]

Our work, in concurrence with other investigators, indicates that liquid-based technique has an improved efficacy for detecting precancerous and cancerous lesions of the cervix when compared with CPS.[5,7,17] After the conversion to liquid-based cytology the detection rates for samples containing atypical cells and cells suspicious for malignancy increased (from 3% to 4.2% and from 1.9% to 2.4%, respectively). Critics may argue that this could be because of an increase in false-positive cases. Mount *et al.* reported no significant difference in rates of false-positive diagnoses between CPS (12.5 %) and LBC (8.4 %).[18] After conversion to LBC, we found the percentage of false-positive tests to be slightly lower than with CPS when looking at the follow-up diagnoses. However, because of the increase in the percentage of samples with abnormal cells found with LBC when compared with CPS, there is an increase in absolute numbers of women with false-positive tests seen in relation to the entire population. Over a period of 18 months with LBC, there were

approximately 700 more women with a false diagnosis of 'atypical cells' and approximately 90 more women with false diagnoses of 'cells suspicious for malignancy' than in the same period of time with CPS.

As mentioned in the section 'Materials and methods', a classification different from the Bethesda classification has been used in this article. Unfortunately, as it is a retrospective study, it has not been possible to subdivide the two diagnostic groups 'atypical cells' and 'cells suspicious for malignancy'. However, in the tables there are explanatory notes making a comparison with the Bethesda classification possible.

We are currently introducing supplementary HPV-testing as a routine procedure on women above 30 years of age with atypical cells, and this we expect will reduce the number of false-positive results. Myers *et al.* argued that specificity is a crucial factor for a test that will be applied to a screening population with mostly negative cases.[19] We agree with Myers *et al.*, and argue that LBC has similar specificity to CPS.

To our knowledge, there has been no change in the incidence of high-risk HPV-infections in Denmark in the years up to the study period, a factor which otherwise could have influenced the results.

The sensitivity of cervical screening is limited to some degree by sampling error, with reported false-negative rates as high as 55%.[20] This sampling error is because of inadequate sampling technique, sampling devices or both. The study of Obwegeser and Brack concludes that there is no statistically significant difference in sensitivity and specificity of CPS and LBC, and that improved detection of cervical abnormalities and better specimen adequacy with LBC is merely a result of improved sampling technique and sampling devices.[21] Critics may claim that this is the case with our study, and that the two study groups cannot be compared with the use of different sampling devices.

Obwegeser and Brack look at conventional smears collected with Ayre spatula alone. In our first study period, the Ayre spatula was always used together with Cytobrush® Plus for endocervix, and according to Martin-Hirsch *et al.* this combination yields an equal or greater percentage of adequate cervical samples and samples with endocervical cells, than with the Cervex- Brush® system that was used in the second study period.[22]

Several investigators argue that the conventional Papanicolau smear technique has serious limitations, in particular a high number of unsatisfactory smears because of obscuring amounts of blood, mucus and inflammation and also air-drying.[5,7,17] Mount *et al.* concluded that wet fixation and liquid-based preparation might enhance visualization of nuclear details, permitting improved detection of chromatin abnormalities.[18] Our study shows similar tendencies, and we can report a decrease of unsatisfactory specimens of 87%, which for a department like ours means somewhere between 1100 and 1200 fewer re-examinations each year.

We have observed an increase in the number of samples without an endocervical component in the LBC samples (8.9%) compared with CPS (8.5%). This has also been noted in earlier publications on liquid-based cytology.[5,23]

It is well known that endocervical cells are typically found clustered in groups in conventional cytological samples, whilst often found one at a time in liquid-based preparation. This makes acknowledgment of endocervical cells more difficult, and could be a reason for the decrease in the endocervical component in the LBC period.

This could be of importance, because of the fact that some investigators argue that high-grade lesions could be associated with endocervical cells.[22] Moreover, it has been suggested that cervical samples without endocervical cells have a higher false-negative rate.[23] Other studies report no significant difference in the detection of cervical lesions in regard to the presence or absence of endocervical cells.[24]

We believe that one of the reasons for the high number of samples lacking an endocervical component in our department is because of suboptimal sample collection and sampling device. We are currently introducing a new type of Cervex-Brush® in an attempt to rectify this problem.

As of today, there are two different semi-automated preparation systems commercially available for liquid-based cytology: SurePath® (TriPath Imaging®) and ThinPrep® system (Cytyc®, Boxborough, MA, USA). Klinkhamer *et al.* argued that only the ThinPrep® liquid-based system showed improved diagnostic efficacy when compared with CPS.[25] In contrast to this, the 2003 NICE report concluded that there is insufficient evidence to recommend one liquid-based screening system over another, and further stated that both systems showed better results than CPS.[15] The SurePath® system was chosen by our department, because of the fact that the brush head of the sampling device is forwarded to the department of pathology in contrast to the ThinPrep® system. Theoretically, all the collected cells are available for evaluation by the cytopathologists with the SurePath® system.

Finally, we agree with Lee *et al.* when they argue the evaluation of liquid-based cytological samples is that more efficient than CPS, due to the smaller area that has to be assessed on the microscope slide and due to the clarity of the specimens.[5] In our laboratory we have experienced an efficiency gain after the conversion to LBC. The preparation of the LBC-specimens is more time consuming compared to the CPS-specimens but the screening is much faster. Each cytotechnician now processes approximately 5500 cervical LBC-samples per year when compared with formerly around 4000 CPS-samples per year (preparation and screening). This has resulted in a 26% reduction of the cytotechnician staff needed in the department with an unchanged number of annually processed cytological samples (from 15 to 11 fulltime jobs). The change in workload as a result of the new settings of the FocalPoint® analyzer has been incorporated in the figures. The absolute numbers of cytotechnicians are not readily comparable with other laboratories as our department is a university department with massive obligations regarding education of cytotechnicians, research, etc.

With the aim of further improving the screening-efficiency, the department is planning to introduce a location-guided screening system (FocalPoint® Guided Screening System).

In conclusion, this study showed the problem of unsatisfactory samples to be significantly reduced with liquid-based cytology when compared with the conventional Papanicolaou smear technique, whereas we observed a slight increase in the number of samples without endocervical component. Our data suggest that there is an increased detection rate of cervical lesions with LBC, meaning that we now diagnose more women with precancerous changes. The specificity of the two techniques seems equal, and the total number of false-positive tests in relation to the whole populations remains high. This means that many women are still unnecessarily worried due to additional cervical investigation. The true specificity of the two techniques cannot be ascertained exactly in this study, because of the fact that it is based upon screening populations, where follow-up of negative cases is not available. The issue of false-positive tests is a recurring problem of screening programmes offered to predominantly healthy populations, and as mentioned above, we hope to be able to improve this aspect of our screening by the help of supplementary HPV-testing.

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