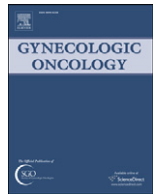




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Superior performance of liquid-based versus conventional cytology in a population-based cervical cancer screening program

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ABSTRACT

Objective. Liquid-based cytology may offer improvements over conventional cytology for cervical cancer screening. The two cytology techniques were compared in a group of 86,469 women who participated in a population-based screening program. Using a nation-wide pathology database containing both cervical cytology and histology records for all patients, we compared the outcome of the two screenings methods with regard to the detection rate of histological proven abnormalities and the determination of the true false-negative rates for both methods.

Methods. Two cohorts of women living in the same geographical region were used. Cohort 1 ($n=51,154$ women) was analysed using conventional cytology (conventional cohort) and cohort 2 (liquid cohort) ($n=35,315$ women) was analysed using liquid-based cytology (SurePath[®]). The samples were processed in one laboratory. The results of histological follow up were available via a central database.

Results. The rate of unsatisfactory slides was significantly lower using liquid-based cytology (0.13% vs. 0.89%, $p<0.0001$). Detection of ASCUS+ (Atypical squamous cells of unknown significance or higher abnormalities) was significantly higher using liquid-based cytology (2.97% vs. 1.64%, $p<0.0001$), mainly due to the increase in the ASCUS category. The percentage of histological abnormalities within the ASCUS samples was approximately equal in both cohorts, indicating that more true abnormal cases were detected using liquid-based cytology. The sensitivity for detection of a histological proven lesion is significantly higher in the liquid cohort compared to the conventional cohort (96.2% vs. 92.0%), with only a slight difference in specificity (97.8% vs. 98.2%).

Conclusion. This population study confirmed previous institution-based reports of decreased numbers of unsatisfactory samples based on liquid-based cytology and showed an increased sensitivity for the detection of cytological abnormalities that was validated by subsequent histological investigation.

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Introduction

Worldwide screening programs for cervical cancer based on the Papanicolaou (PAP) smear have contributed to the decrease in incidence and mortality of cervical cancer [1]. Nevertheless, both false-negative and false-positive results due to sampling and screening errors are well-recognized problems. Liquid-based cytology was introduced as an alternative to conventional cytology screening in the hope of improving specimen adequacy and sensitivity in detecting cervical abnormalities. Various studies have shown that liquid-based cytology is more effective in the detection of cervical intraepithelial neoplasia (CIN), reduces the number of unsatisfactory specimens, and reduces screening time compared to conventional cytology [2–13].

A nationwide, government-sponsored cervical screening program has been operative in the Netherlands for more than 25 years. All asymptomatic women between 30 and 60 years of age are invited by the local health authorities to participate in this screening program. At 5-year intervals cervical cytology samples are taken by general practitioners and sent to regional pathology laboratories. In the region of Southwest Holland, 56% of women within the defined population participate in the program [14,15]. Ninety five percent of the smears are sent to one laboratory. Despite this quality-controlled, well-organised, population-based screening program, the proportion of false negative smears is about 20% [16]. Therefore, we introduced a liquid-based cytology system (SurePath[®], BD Diagnostics, Tripath, Burlington, NC 27215 USA) in this region in 1997 to study the effectiveness of this method in comparison with conventional cytology.

We investigated the sensitivity and specificity of these two screening techniques in a group of 86,469 women participating in a

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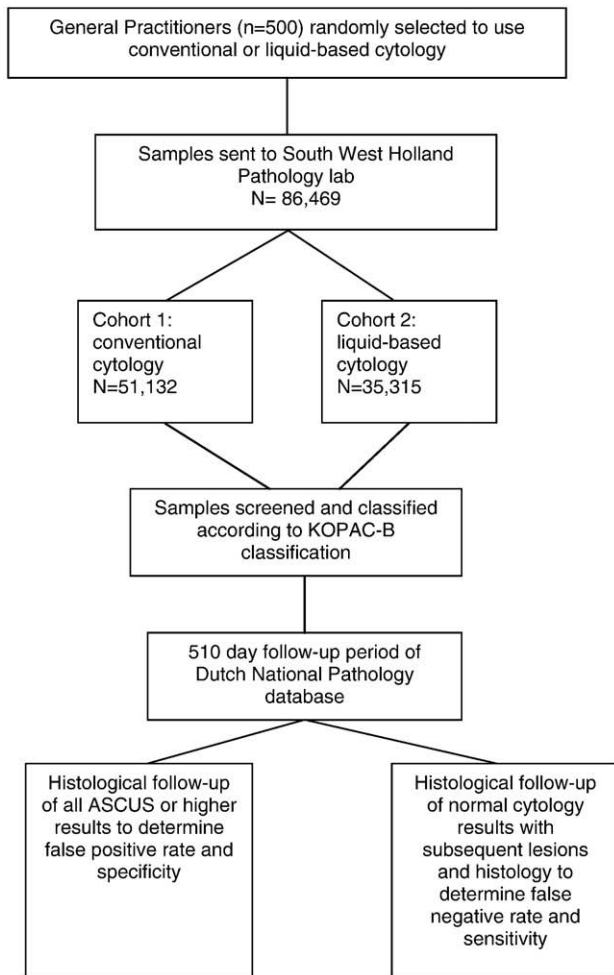


Fig. 1. Sample collection from the Netherlands screening program and follow-up of subjects, July 1997–June 2002.

population-based screening program. We compared the outcome of the two screening methods with regard to the detection rate of histological abnormalities. The false negative rate was investigated using our nationwide pathology database containing both cervical cytology as well as histology results for all women. By using this database we were able to achieve 100% of follow-up in cases with subsequent biopsies.

Materials and methods

Patients and screening methods

This study was conducted in one pathology laboratory in South-west Holland that screens Pap specimens obtained from approximately 500 general practitioners. The material consisted of samples from asymptomatic 86,469 women (age 30–60) participating in the national screening program, collected during the period July 1997–June 2002. This age window was chosen as a result of the inclusion criteria put forward by the national screening program. The women chosen were a-symptomatic according to the entry criteria as assessed by the general practitioner according to a medical checklist. HPV DNA-testing was not used as a triage method in the study time window. In case of ASCUS results, subsequent patient management did not use any HPV-testing data. Cervical samples were taken by general practitioners randomly selected to use either conventional or liquid-based cytology using the same brush technique (Rovers® Cervix-Brush®) for obtaining samples. This is a commercially available brush.

The tip of the brush was removed after the smear has been made and is completely put in a disposable collection vial (SurePath®, TriPath Imaging, Inc., Burlington NC, USA). After consenting to the study, the general practitioners involved used consequently one of the sampling techniques throughout the study. There was no pre-selection for age or demographic distribution of adherent patient population when selecting the general practitioners. All physicians/practitioners selected to use the liquid-based technique were instructed on the manufacturer's policies and procedures. All patients participating in the screening program consented to use their data for research purposes. All data were treated according to the Dutch national ethical guidelines for use of medical data.

The conventional smears were prepared according to standard laboratory protocols and stained with the Papanicolaou stain. The liquid-based specimens were collected using the SurePath® disposable collection vials from TriPath Imaging (Burlington, USA). The slides were prepared according to the manufacturer's guidelines. Subsequently, the slides were screened by cytotechnologists and classified according to the KOPAC-B classification, the standard classification system used in the Netherlands (NVVP guidelines). All abnormal smears of ASCUS or higher were reviewed by experienced cytopathologists (HB, VK). All KOPAC-B classifications were converted to the Bethesda classification for this study according to the translation published in the Dutch cervical screening guidelines [17]. The participating cytotechnicians and cytopathologists were trained in the interpretation of liquid-based cytology prior to the start of this study.

Cytology-Histology correlation and follow-up

In the Netherlands, the outcome of each cytological and/or histological investigation is submitted to the Dutch Network and National Database for Pathology (PALGA). As a result, all Dutch pathology and cytology departments are interconnected for 100% of cytology and histology specimens. This enables a unique population-based study with nearly 100% correlation. The histological follow-up of all patients with a cytological classification of ASCUS or higher was retrieved from the PALGA database. To determine the true false-negative rate of the screening results, we collected the data from all patients with a negative cytology (i.e., within normal limits), but with a histological proven cervical lesion (CIN 1 or higher). Here the conclusions of the histological reports were used, as it was ethically not allowed to break the anonymisation code in order to retrieve and review the cases diagnosed in other centres.

To ensure that all patients had the same follow-up period, an end point of 510 days was arbitrarily chosen and all cases were closed after this follow-up period. The histological results were classified as: no

Table 1

Cytological classifications: comparison between conventional cytology (Cohort 1) and liquid-based cytology (Cohort 2)

	Cohort 1 Conventional N=51,132 n (%)	Cohort 2 Liquid-based N=35,315 n (%)	p-value*
Unsatisfactory	435 (0.89)	46 (0.13)	<0.0001
Within normal limits	49856 (97.47)	34219 (96.9)	<0.0001
Abnormal (ASCUS or higher)	845 (1.65)	1052 (2.98)	<0.0001
ASCUS	443 (0.87)	730 (2.07)	<0.0001
LSIL	110 (0.22)	94 (0.27)	0.1284
HSIL	288 (0.56)	226 (0.64)	0.1493
Squamous cell carcinoma	4 (0.008)	2(0.006)	0.2068
Endocervical cells	44411 (86.17)	32328 (89.01)	<0.0001**

* p-value was given by Cochran-Mantel-Haenszel test controlling for abnormal cytology (ASCUS, LSIL, HSIL).

** p-value determined using Chi-square test.

Table 2

Correlation between cytological and histological data: conventional cytology (Cohort 1) versus liquid-based cytology (Cohort 2)

Cytology	Cohort 1 Conventional N=51,132			Cohort 2 Liquid-based N=35,315			p-value(CIN 1+)
	Histology			Histology			
	Normal/none		CIN 1+	Normal/none		CIN 1+	
	N	n (%)		N	n (%)		
Unsat	435	432 (99.31)	3 (0.69)	46	46 (100)	0	1.0
Within normal limits	49,856	49,826 (99.94)	30* (0.06)	34,219	34,207 (99.96)	12** (0.04)	0.1183
Abnormal ASCUS	443	396 (89.39)	47 (10.61)	730	657 (90)	73 (10.0)	0.7384
LSIL	110	57 (51.82)	53 (48.18)	94	50 (53.19)	44 (46.81)	0.8448
HSIL	288	44 (15.28)	244 (84.72)	226	36 (15.93)	190 (84.07)	0.8398
Squamous cell carcinoma	4	1 (25.00)	3 (75.00)	2	0 (0.00)	2 (100.00)	1.0

* 21 of the 30 cases (70%) were CIN 2 or higher.

** 7 of the 12 cases (58%) were CIN 2 or higher.

histology available, histology not representative (transformation zone not present in the biopsy), no dysplasia, CIN 1, 2 or 3, squamous carcinoma, or adenocarcinoma. All endometrial carcinomas were excluded from the analysis. The collection and review process is shown in Fig. 1.

Statistical analyses

P-values comparing histology and cytology were determined by the Cochran-Mantel-Haenszel test. False negative and false positive rates were compared using the 2-sided Fisher's exact test.

Results

Patient characteristics

Samples were collected from 86,469 women between the ages of 30 and 60. The study cohorts consisted of 51,154 conventional smears (conventional cohort) and 35,315 liquid-based cytology slides (Cohort 2). There was no difference in age-distribution between the two cohorts (average 43.9 years vs. 43.7 years of age).

Cytology

Cytology results within the two cohorts are shown in Table 1. The percentage of unsatisfactory slides based on liquid-based cytology (Cohort 2) was significantly less compared to conventional cytology screening (Conventional cohort) (0.13% vs. 0.89%, $p < 0.0001$). The percentage of satisfactory specimens containing endocervical cells was higher in the liquid cohort compared with the conventional cohort (89.01% vs. 86.17%, $p < 0.0001$). Significantly more samples were classified as ASCUS or higher in the liquid cohort than in the conventional cohort. (2.97% vs. 1.64%, $p < 0.0001$). This increase was driven by an increase in the percentage of ASCUS detected in the liquid cohort compared to the conventional cohort (2.07% vs. 0.87%; $p < 0.0001$), while the percentages of LSIL (low grade intraepithelial neoplasia) and HSIL (high grade intraepithelial neoplasia) lesions and (either adeno-, or squamous cell) carcinoma were similar between the cohorts (the ASCUS/LSIL+ ratio in the liquid cohort vs. the conventional cohort: 2.28 vs. 1.11, $p < 0.0001$).

Results of correlation with histology

The correlation between histological follow-up data, within the study period, and cytological classifications is shown in Table 2. The percentages of ASCUS, LSIL, and HSIL cytology samples showing normal and CIN 1+ histology are similar in the two cohorts. The false-positive rate (abnormal cytology but benign histological follow-up), determined from the patients with abnormal cytology, but normal histology follow-up, was significantly higher in the liquid cohort compared to the conventional cohort (2.25 vs. 1.83, $p < 0.0001$) (Table 3).

A very small number of patients with a negative cytology (i.e., within normal limits) were found to have unforeseen histology performed within the window of follow up. This was not intended by the screening program, but these data became available using our national database, which has 100% coverage of pathology data, and we felt that review of these cases could lead to potential insight into false negative screening results. Data from all patients in our region with a negative cytology (i.e., within normal limits), but with a histological proven cervical lesion (CIN 1 or higher), were reviewed to determine the true false negative rate. In the conventional cohort, 30 patients (0.06%) with cytology results within normal limits had subsequent histology within 510 days showing CIN 1 or higher lesions. In the liquid cohort, 12 patients (0.04%) with normal cytology were identified with CIN 1, or higher lesions in histology. In both cohorts, the majority of these false negative lesions were CIN 2 or higher (21/30, 70%, in the conventional cohort and 7/12, 58%, in the liquid cohort). The false-negative rate for the liquid cohort analysed by liquid-based cytology was significantly lower than for the conventional cohort (3.76% vs. 7.96% relative to total CIN1+ lesions), $p = 0.0247$. The sensitivity for detection of a histological proven lesion (CIN 1+) is significantly higher in the liquid cohort (LBC) compared to the conventional cohort (CC) (96.24; 95% CI 93.54–97.84 vs. 92.04; 95% CI 88.87–94.37). The same was true for the detection of CIN 2+ lesions using liquid-based cytology (97.19%; 95% CI 94.31–98.63 vs. 93.46%; 95% CI 90.21–95.68).

Discussion

A Nation-wide screening program for cervical cancer has been operative in the Netherlands since 1975. Although this program is well controlled and uses skilled cytotechnologists, a false-negative rate of about 20% for HSIL or higher lesions has been observed [16]. Methods to reduce the false-negative rate were investigated including the introduction of liquid-based cytology.

Various studies have reported the advantages of liquid-bases cytology over conventional cytology [2–13] but controversies remain.

Table 3

Sensitivity and specificity and comparison of false negative and false positive rates for conventional and liquid-based cytology

	Cohort 1 Conventional % (95% confidence interval; n)	Cohort 2 Liquid-based % (95% confidence interval; n)	Change %	p-value*
Sensitivity	92.04 (88.87, 94.37)	96.24 (93.54, 97.84)		
Specificity	98.17 (98.05, 98.28)	97.75 (97.58, 97.90)		
False negative rate	7.96 (30/377)	3.76 (12/319)	-4.2	0.0247
False positive rate	1.83 (929/50,755)	2.25 (789/34,996)	0.42	<0.0001

Rates and sensitivity and specificity estimates were made including unsatisfactory specimens and using CIN 1+ as the cut off.

* Test was performed by 2-sided Fisher's exact test.

Many studies had methodological deficiencies including inadequate follow-up of negative cytology [17,18]. A recent review highlights the need for large scale randomised controlled trials. These trials should at least incorporate a biopsy of women who have abnormal results in liquid-based cytology or in conventional cytology and a histology read without the knowledge of cytology results as a reference standard [18].

All women who enter the screening program give a written consent that their personal data and results may be used for scientific purposes. We undertook a cohort study of women in the same age group, randomly chosen to participate either in the LBC or the CC group. A furthermore distinguishing feature of the Dutch screening program is that all cytology records and any subsequent histological reports of all the women who participate in the study are stored in a national database (PALGA). Therefore, all patients with normal cytology are available for follow-up if they have subsequent abnormal cytology and/or histology results. The availability of these data permitted the examination of true false-negative rates of cytological screening, in contrast to other studies [19–23]. Previous studies typically have used selective follow-up of subjects with cytological positive-, or negative samples, which can introduce verification bias. This is the largest study that has been able to compare the true false-negative rates for conventional and liquid-based cytology screening methods in a population-based manner. Other studies that have avoided verification bias have been conducted using smaller numbers of subjects [19–23].

Another unique facet of this study is the sampling device, which has been identical in both cohorts, unlike many other studies [18]. In our region in the Netherlands, the Cervix Brush® has been the preferred sampling device for more than 10 years. Therefore, all observed differences could only be related to preparation technique; the effect of sampling technique can be excluded.

A reported advantage of liquid-based cytology over conventional Pap screening is the marked decrease in the number of unsatisfactory slides [2–13]. This improvement for SurePath® liquid-based cytology is related to the fact that 100% of the collected sample is transferred to the fluid vial and that the cell enrichment process reduces obscuring material, such as blood, mucous and inflammatory cells [9,24–26]. The present report confirmed a reduction in the percentage of unsatisfactory slides of approximately 75% in the liquid-based cytology group compared to the conventional cytology group. Moreover, we can confirm that the time needed for liquid-based cytology screening is reduced by more than 50% compared with a conventional smear, as previously reported (data not shown) [6,9,27]. This is due to multiple factors including the 13 mm circle of stained cells, a smaller screening area than found in a conventional smear; the optimal preservation and staining of cellular material, eliminating the additional screening time required with conventional smears due to air drying artefacts; and the reduction or elimination of obscuring factors.

The most striking result of the present study is the significant increase in detected ASCUS cases in the liquid cohort compared to the conventional cohort, with no significant difference in the LSIL or HSIL detection rate between the two groups. This is in contrast with other published studies, that while, likewise also reporting an increased ASCUS detection rate using liquid-based cytology, they also found an increased rate of LSIL+ detection, resulting in a reduced ASCUS/LSIL+ ratio [6,7,8,27,28]. Not only did we find an increased number of ASCUS cases, using liquid-based cytology in this study, but also the percentage of histological abnormalities within these ASCUS samples was approximately equal in both cohorts, indicating that more true abnormal cases were detected using liquid-based cytology. Other studies have demonstrated a temporary increase in ASCUS rates, with a concomitant decrease in HSIL detection, in the first 6 months after conversion from conventional Pap to liquid-based cytology [10,13]. This phenomenon

was attributed to the “learning curve” in the interpretation of liquid-based cytology, as follow-up tissue correlation data confirmed that several HSIL cases had been classified as ASCUS, and that HSIL rates normalized after the initial 6 month training period. Since we looked at several thousands of LBC samples before the study started, we feel we were quite advanced in the ‘learning curve’. The availability of liquid-based cytology at relatively low costs could be of interest in screening programs in the developing countries. Alternatively it is a step forward for those screening programs in general, which does not have a HPV DNA testing as a standard in the triage of high-versus low-risk patients.

The availability of all cytological and histological reports of each laboratory in the PALGA nationwide central database enabled us to trace the histology of originally false negative cases, independent of the location of the laboratory where subsequent histology was obtained. The false-negative rate for the liquid-based cytology cohort was lower than the conventional cytology cohort. Within the arbitrary study limit of 510 days, and using a histological CIN 1+ lesion as an endpoint, the false negative rate for conventional cytology was approximately twice as high as for liquid-based cytology. As a result, sensitivity was significantly greater in the liquid-based cytology cohort compared to conventional cytology (96% versus 92%). The majority of false-negative cases were CIN 2 or higher. Although there was a minor difference in the occurrence rate of squamous cell carcinomas between the two study groups, this was not statistically significant ($p=0.2068$). This p-level virtually excludes a baseline-bias between the two groups.

In summary, liquid-based cytology had superior performance compared to conventional cytology within a nationwide screening program setting in the Netherlands. The study confirmed previous reports of decreased numbers of unsatisfactory samples with liquid-based cytology, increased numbers of samples including endocervical cells, and showed an overall decrease in the false-negative rate and increased sensitivity that was validated by subsequent histological investigation.

Conflict of interest statement

The authors do not declare any conflict of interest, nor any financial support by SurePath®, TriPath Imaging, Inc., Burlington NC, USA for performing this study.

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