

## Comparison of conventional and liquid-based cytology: do the diagnostic benefits outweigh the financial aspect?

Erdin İLTER<sup>1</sup>, Ahmet MİDİ<sup>2</sup>, Berna HALILOĞLU<sup>1</sup>, Aygen ÇELİK<sup>1</sup>, Arzu Neşe YENER<sup>2</sup>, İpek ULU<sup>1</sup>, Hayriye Serpil BOZKURT<sup>1</sup>, Ümit ÖZEKİCİ<sup>1</sup>

**Aim:** We aimed to compare the efficiency of conventional cytology (CC) and new liquid-based cytology (LBC) techniques in the assessment and the accuracy of Pap smears reported as abnormal by histological examinations.

**Materials and methods:** A total of 3488 women who were undergoing routine cervical screening (1308 CC and 2180 LBC) were included in the initial screening. The results were assessed as either satisfactory or unsatisfactory. Satisfactory results were subdivided as negative, atypical squamous cells of undetermined significance (ASCUS), atypical squamous cells for which high-grade lesions could not be excluded (ASC-H), low-grade squamous intraepithelial lesion (LGSIL), high-grade squamous intraepithelial lesion (HGSIL), and cancer.

**Results:** These data show that the rate of unsatisfactory results for the LBC technique (0.05%) was lower than for the CC group (0.5%). Except for ASCUS and cancer cytology, all other atypical cytology results were diagnosed more frequently with CC than with LBC. The rates of detected ASC-H and HGSIL were higher with CC than LBC, and the difference was statistically significant ( $P < 0.05$ ).

**Conclusion:** LBC has higher satisfaction rates than CC. LBC also detected more true-abnormal cases when compared with CC. The residual specimens from the LBC technique can be used to detect human papillomavirus DNA through immunocytochemistry, if needed. However, the benefits of LBC do not seem to justify the cost. It seems that CC should be the first choice for developing countries with lower incomes.

**Key words:** Papanicolaou smear, liquid-based cytology, cervical cytology, epithelial abnormalities

### Introduction

Cervical cancer is one of the most common female malignancies with a high mortality rate in developing countries (1).

Since the introduction of the Papanicolaou (Pap) smear in the last 60 years, mortality from cervical cancer has decreased by 70%–80% in developed countries. In underdeveloped countries that have no regular Pap screening programs, 80% of invasive cervical cancer still occurs (2,3). Additionally, the test is also widely used for the diagnosis of some genital tract infections (4).

Although conventional cytology (CC) contributed to the decrease in cervical cancer mortality rates, issues with consistency overshadowed the benefits. CC smears are prepared by directly smearing collected cervical cells onto a glass slide; in order to preserve the sample, it must be transferred to the slide quickly. In addition to clumping or cells overlapping on the slide, abnormal cells may also be obscured by blood, mucus, and other debris, which potentially leads to an increase in false-negative and equivocal (i.e. ASCUS) results (5).

Several new technologies have recently been introduced in an attempt to decrease the occurrence of

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<sup>1</sup> Department of Gynecology, Faculty of Medicine, Maltepe University, İstanbul – TURKEY

<sup>2</sup> Department of Pathology, Faculty of Medicine, Maltepe University, İstanbul – TURKEY

**Correspondence:** Erdin İLTER, Department of Gynecology, Faculty of Medicine, Maltepe University, İstanbul – TURKEY  
E-mail: erdinilter@hotmail.com

false-negative results due to problems with sampling, screening, and interpretation. Slide-preparation techniques that use a fluid medium such as liquid-based cytology (LBC) have been developed to overcome these limitations by producing thin layers of smears. However, for many reasons, including aggressive marketing, these technologies have replaced the apparently less expensive conventional Pap smear. According to reports, this change has dramatically made a 60% increase in national expenditure (6).

We aimed to compare the efficiency of CC and LBC in the cytological assessment of the cervical epithelium and their respective financial aspects. We also evaluated the accuracy of these methods in identifying Pap smears reported as abnormal using histological confirmation.

### Materials and methods

The study was conducted at Maltepe University Hospital between January 2006 and January of 2010. A total of 3488 women without a history of cervical dysplasia or genital malignancy who were undergoing routine cervical screening were included in the study. Pregnant women and patients who previously experienced hysterectomy were excluded from the study. Of the participants, 1308 women were screened by CC and the other 2180 by LBC. Histological examinations were performed for women with abnormal cervical cytology.

Two different cervical samples were taken by gynecologists using the same brush technique for obtaining samples. Conventional samples were collected, smeared onto the slide, and immediately fixed with polyethylene glycol. For LBC samples, the tip of the brush was removed after the smear had been taken and was completely immersed in a disposable collection vial (PapSpin™, Thermo Shandon, Pittsburgh, Pennsylvania, USA). The cost to examine 1 conventional sample only was about US\$1, while 1 liquid-based sample was nearly \$8. The results were assessed as either satisfactory or unsatisfactory. Satisfactory results were based on the Bethesda system (7) and subdivided as negative (including atypia, favor reactive), squamous cell atypia (atypical squamous cells of undetermined significance [ASCUS] and atypical squamous cells for which high-grade lesions could not be excluded [ASC-H]) (Figure), low-grade squamous intraepithelial lesion (LGSIL), high-grade squamous intraepithelial lesion (HGSIL), squamous cell carcinoma (SCC), and adenocarcinoma. Of the participants with abnormal cytological results, 37.7% (48/127) agreed to and underwent colposcopy-directed cervical biopsy and were categorized according to World Health Organization classification of squamous lesions in 3 classes: CIN 1, 2, and 3 (8).

### Results

#### Patient characteristics

The mean age of all participants was  $39 \pm 11$  years (range: 18 to 72). There was no difference in age

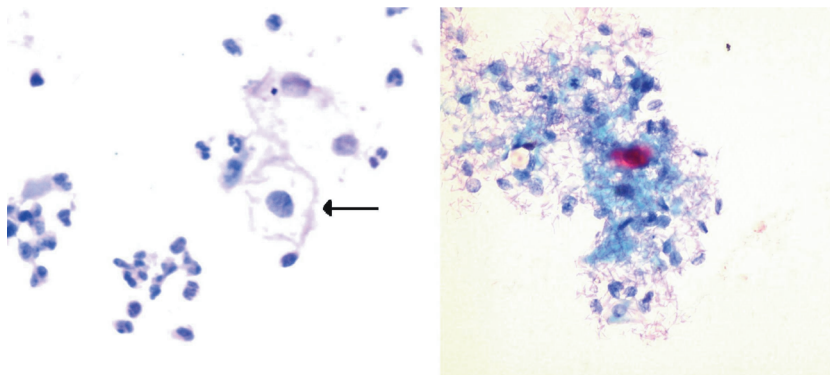


Figure. Squamous epithelial cells with enlarged, mildly hyperchromatic nuclei with nuclear contour irregularities. Nucleus-to-cytoplasm ratio is preserved (left side). ASC-H; squamous cell clusters with enlarged, irregular, hyperchromatic nuclei. Nucleus-to-cytoplasm ratio is minimally increased (right side). Pap stain, 400× original magnification.

distribution between the 2 groups (CC group average: 39.4 ± 11 years; LBC group: 39.1 ± 11 years). The study period was between January 2006 and January 2010, and 3488 smears were entered into the database (1308 conventional Pap smears and 2180 LBC samples). The reason for the uneven distribution of the 2 methods was related to the pathology department policy. Between 2006 and 2008, the department preferred the conventional method for all samples. After that period, the department changed to the LBC method.

**Cytology**

Cytological findings and comparison of the smear results for LBC versus CC are listed in Table 1.

These data show that the rate of unsatisfactory results for the LBC technique (0.05%) was lower than that for the CC group (0.5%) (P < 0.001). The main causes for CC inadequacy were samples being obscured by red blood cells. For the LBC slides, the only cause was the presence of massive red blood cells.

The numbers and rates of epithelial abnormalities detected by LBC and CC were, respectively: ASCUS, 57 (2.6%) and 28 (2.1%); ASC-H, 1 (0.045%) and 1 (0.07%); LGSIL, 18 (0.8%) and 17 (1.3%); HGSIL, 1 (0.045%) and 1 (0.07%); and SCC, 2 (0.09%) and 1 (0.07%). Except for ASCUS and cancer cytology, all atypical cytology results were diagnosed more frequently with CC than with LBC. The rates of detected ASC-H and HGSIL were higher with CC

than with LBC, and the difference was statistically significant (P < 0.05).

We also analyzed 3 cytodiagnostic thresholds, ASC+ (including ASCUS, ASC-H, LGSIL, HGSIL, and carcinoma), LGSIL+ (including LGSIL, HGSIL, and carcinoma), and HGSIL+ (HGSIL and SCC), to compare the LBC study group to the CC group. The numbers and rates of epithelial abnormalities detected by LBC and CC were, respectively: ASCUS+, 79 (3.6%) and 48 (3.6%); LGSIL+, 21 (0.9%) and 19 (1.4%); and HGSIL+, 3 (0.13%) and 2 (0.14%).

**Histology**

A colposcopic examination was recommended for all patients with epithelial abnormalities. Only 37.7% (48/127) of the participants with abnormal cytological results agreed to and underwent colposcopy-directed cervical biopsy.

**LBC and histology**

Twenty-seven of 79 (34.1%) participants agreed to be examined by colposcopy and biopsy from the LBC group. The test was done for 14 ASCUS, 11 LGSIL, and 2 SCC cases. The results for the colposcopic examination are summarized in Table 2. The 2 cases of SCC cytological findings were confirmed by histology. Eleven of 14 ASCUS cytology results were normal according to the histology. The remaining 3 participants had CIN 2 histology in the biopsies. Only 5 of 11 LGSIL results were normal according

Table 1. Comparison of LBC and CC results.

	LBC: number (percentage)	CC: number (percentage)
<b>Total</b>	2180	1308
<b>Satisfactory</b>	2179 (99.95%)	1301 (99.5%)
<b>Unsatisfactory</b>	1 (0.05%)*	7 (0.5%)
<b>ASCUS</b>	57 (2.6%)	28 (2.1%)
<b>ASC-H</b>	1 (0.045%)	1 (0.07%) ¶
<b>LGSIL</b>	18 (0.8%)	17 (1.3%)
<b>HGSIL</b>	1 (0.045%)	1 (0.07%) ¶
<b>SCC</b>	2 (0.1%)	1 (0.07%)
<b>ASC+</b>	79 (3.6%)	48 (3.6%)
<b>LGSIL+</b>	21 (0.9%)	19 (1.4%)
<b>HGSIL+</b>	3 (0.1%)	2 (0.1%)

\* P < 0.001, ¶ P < 0.05.

Table 2. Histopathological findings of abnormal cytology results for LBC and CC.

	Normal	CIN 1	CIN 2	CIN 3	SCC	Total
LBC ASCUS	11 (78.6%)	-	3 (21.4%)	-	-	14
CC ASCUS	9 (81.8%)	1 (9.1%)	1 (9.1%)	-	-	11
LBC ASC-H	-	-	-	-	-	-
CC ASC-H	-	-	-	-	-	-
LBC LGSIL	5 (45.4%)	3 (27.3%)	2 (18.2%)	1 (9.1%)	-	11
CC LGSIL	5 (62.5%)	2 (25%)	1 (12.5%)	-	-	8
LBC HGSIL	-	-	-	-	-	-
CC HGSIL	-	-	-	1 (100%)	-	1
LBC SCC	-	-	-	-	2 (100%)	2
CC SCC	-	-	-	-	1 (100%)	1
LBC ASCUS+	16 (59.2%)	3 (11.1%)	5 (18.6%)	1 (3.7%)	2 (7.4%)	27
CC ASCUS+	14 (66.7%)	3 (14.3%)	2 (9.5%)	1 (4.7%)	1 (4.7%)	21
LBC LGSIL+	5 (38.4%)	3 (23.1%)	2 (15.4%)	1 (7.7%)	2 (15.4%)	13
CC LGSIL+	5 (50%)	2 (20%)	1 (10%)	1 (10%)	1 (10%)	10
LBC HGSIL+	-	-	-	-	2 (100%)	2
CC HGSIL+	-	-	-	1 (50%)	1 (50%)	2

to the histology. Of the others, 3 were CIN 1, 2 were CIN 2, and 1 was CIN 3 according to the histological process.

### CC and histology

From the CC group, 21 of 48 (43.7%) participants agreed to be examined by colposcopy and biopsy. The colposcopic examination was performed for 11 ASCUS patients, 8 LGSIL patients, 1 HGSIL patient, and 1 SCC patient. The results for the colposcopic examinations are summarized in Table 2. The CC results were supported 100% by colposcopy-directed cervical biopsy in patients with HGSIL and cancer. The patients with HGSIL cytology had CIN 3 results, while patients with cancer cytology had SCC results from the histological process. One CIN 1 and 1 CIN 2 case were histologically confirmed from the 11 ASCUS cytology patients. Of 8 LGSIL patients, 5 were histologically normal. The remaining 3 patients had CIN 1 in 2 cases and CIN 2 in 1 case.

### Financial examination

The cost for 1 conventional cytology examination is \$1, and the cost is \$8 for the LBC method. At our hospital, the average number of cytology examinations performed in a year is nearly 1000. Thus, the cost of CC and LBC for 1 year is \$1000 and \$8000, respectively. The cost for 1 colposcopy is nearly \$250. In our study, 79 (3.6%) patients from the

LBC group had abnormal results and were referred for a colposcopy. The numbers were also similar in the CC group (48 [3.6%]). This means that 36 patients should be referred for a colposcopy, costing \$9000. Not all cytologically determined abnormal results had histological confirmation. Only 41% of LBC samples and 34% of CC samples were histologically confirmed. Therefore, 21 and 24 patients per year for LBC and CC, respectively, underwent unnecessary colposcopic investigation stemming from positive cytologic but negative histologic results.

### Discussion

An ideal screening test for cervical lesions should have both perfect sensitivity and specificity. As we know, such a test is not available. The screening test should have high sensitivity, such that no lesion would escape detection at the expense of a somewhat diminished specificity. Any positive results at the initial screening, including ASCUS and higher lesions, need further investigation to confirm or rule out disease diagnoses. Conventional cytology is known to have low sensitivity (70%–80%), attributed to inadequate sample collection and interpretation difficulties (9). However, the higher sensitivity of liquid-based cytology (85%–95%) has been well documented (10–13).

Since the 2 different smear-group populations were collected during different time periods, we evaluated the demographic data comparison to assess their similarities and differences. This comparison of the patient populations with regard to age demonstrated that the 2 populations were reasonably enough alike to allow comparison of other population parameters.

### **Satisfactory**

A reported advantage of liquid-based cytology over conventional Pap screening is the marked decrease in the number of unsatisfactory slides (14–17). We demonstrated that only 1 of 2180 LBC examinations was insufficient, whereas 7 of 1308 CC were unsatisfactory. The rate of definite diagnosis by LBC seems to be a little higher than that by CC because of better fixation and sampling of the squamocolumnar junction ( $P < 0.001$ ). The adequate results for LBC and CC were 99.9% and 99.5%, respectively. Our results were consistent with recent studies. Longatto Filho et al. (18), Monsonogo et al. (12), and Beerman et al. (19) found similar results for LBC: 98.6%, 99.4%, and 99.8%, respectively. The present report also confirmed a reduction of approximately 90% in the percentage of unsatisfactory slides in the liquid-based cytology group (0.05%) compared to the conventional cytology group (0.5%). Similar results were detected by Williams (20), who reported that the rate of unsatisfactory smears fell from 13.6% to 1.9% when screening changed from CC to LBC and that colposcopic referrals for repeated unsatisfactory smears fell from almost 25% to 0.5%.

### **Abnormal results**

An important result of the present study is the increase in detected ASCUS cases in the LBC group (2.6%) compared to the CC group (2.1%), with the opposite in LGSIL results (0.8% for LBC and 1.3% for CC). Recently Davey et al. (21) reviewed 56 studies and found higher rates for detection of ASCUS in LBC examination (4.0% for LBC and 3.8% for CC). Davey et al. also demonstrated that LBC classified more slides as LGSIL (2.6% for LBC and 1.4% for CC) and HGSIL (0.9% for LBC and 0.6% for CC) than did CC, which was not supported by our results.

Previously, Colgan et al. (15) found an ASC+ rate of 4.6% for LBC and 3.8% for CC, an LGSIL+ rate of 2.1% for LBC and 1.5% for CC, and an HGSIL

rate of 0.3% for LBC and 0.3% for CC. In the present study, the detection rates for ASC+ lesions with both techniques were same: 3.6% for LBC and 3.6% for CC. With respect to LGSIL+, the detection rate for the LBC study group (1%) was lower than that for the CC group (1.4%). This finding of a decreased detection rate at an LGSIL+ threshold for the LBC technique is not consistent with the findings of Colgan et al. Although the LGSIL+ rates were lower in the LBC group, the histological confirmation was higher than for CC (61% for LBC vs. 50% for CC). This indicated higher histologically proven abnormal cases for LBC than CC. Of 13 LGSIL+ cases in the LBC group, 8 (61%) showed abnormal epithelial colposcopic biopsy results. There were no distinct differences in the detection rate of HGSIL+ in the LBC study group (0.13%) compared with the CC group (0.14%). Past studies' results for HGSIL+ lesions are conflicting. Some have demonstrated an increased detection rate of LBC for HGSIL+ relative to the conventional test (22,23), whereas others have been unable to demonstrate this relative advantage in sensitivity (24,25).

The percentage of histological abnormalities within the ASCUS samples was approximately equal in both groups (LBC, 21% vs. CC, 19%), which also indicated that more true-abnormal cases were detected using LBC. Similar results were detected in LGSIL cases. Of the LGSIL cases in the LBC group, 54.5% were proven to be abnormal upon histology examination, while only 37.5% of LGSIL cases in CC were abnormal, indicating more true-abnormal results for the LBC group.

In the present study, for women that had ASCUS as determined by CC screening, the risk of having histologically confirmed CIN 2 or 3 was estimated to be 9%, or 12.5% if the patient was found to have LGSIL. The same results for LBC screening were 21% and 18% for ASCUS and LGSIL, respectively. Baker (26) also found the prevalence of histologically confirmed CIN 2 or 3 in women with atypical squamous cells to be between 5% and 17%. Gazvani and Öztürk (27) reported that 27% of patients with cytologically suspected LGSIL were diagnosed as having CIN 2 or 3, which required a more careful follow-up.

The detection rates for HGSIL cytology were very low for both methods (0.045% for LBC and 0.07% for CC). The histological confirmations for HGSIL and cancer cytology were similar in both groups. One HGSIL and all cancer cases in the CC group were consistent with histology results (CIN 3 and cancer). Two cancer cases in the LBC group were also diagnosed as cancer upon histology.

The study had a significant limitation. It was a retrospective, observational study that was planned after new Papanicolaou test LBC screening was conducted by the pathology department starting in 2008. The previous CC group was also drawn from the same laboratory and similar populations, but overall, it was not a preferred perfect randomized control group.

Financial examination should be an important part of this kind of study. Previously, Raab et al. (28) estimated an additional annual cost of nearly \$2.5 billion for the United States if LBC were used for every sample rather than the conventional smear. They assumed an additional \$10 cost per every LBC. At our hospital, this additional cost is nearly \$7. The average number of cytology examinations performed per year is 1000. Our financial loss after LBC is \$7000 per year, representing what we lose by choosing LBC rather than the conventional method. It is therefore important to calculate what can be earned by using LBC. We found that 36 patients (3.6%) had abnormal results as determined by CC and LBC per 1000 samples. According to our colposcopic results, 66% of abnormal cytology results determined by CC were false positives with negative results by histological confirmation. This means that 24 patients per 1000 CC samples underwent unnecessary colposcopic examination. On the other hand, 59% of abnormal cytology was false-positive according to colposcopic results for LBC. Therefore, 21 patients per 1000 LBC samples had an unnecessary colposcopic examination. According to these results, LBC only decreased the

number of unnecessary colposcopic examinations by 3 per year, which would save only \$750. Based on the parameters of our study, the use of LBC comes with a loss of \$6250 every year. Of course, this seems like a small loss for one hospital, but this money could be used to protect 20 adolescents from cervical cancer by providing human papillomavirus (HPV) vaccinations. According to GLOBOCAN data (29), supported by an investigation by the Department of Cancer Control of Turkey's Ministry of Health, the national cervical cancer incidence is 4.5 in 100,000. It is estimated that we will encounter 1500 new cervical cancer cases in 1 year, as the population is nearly 70 million. There are nearly 1000 hospitals affiliated with the Ministry of Health in Turkey. Although we assume that the cytological samples taken per year by those hospitals total more than those taken at university hospitals, if we calculate the average annual examinations to be 1000 as at our hospital, the financial loss across the country may represent the cost of providing 20,000 adolescent girls with an HPV vaccination, serving 7 times more women than cervical cancer subjects per year.

In summary, LBC has some advantages when compared to CC. First of all, LBC has higher rates of satisfactory results than CC. Fewer repeat screenings are needed when using LBC. LBC also detects more true-abnormal cases when compared to CC. LBC provides shorter screening time when compared to CC. This is one of the most important points that makes LBC preferential over CC for many pathologists. Finally, perhaps the most important difference between LBC and CC is that the residual specimens from the LBC technique can be used for immunocytochemistry and detection of HPV DNA, if needed. This is impossible with CC samples. Despite these advantages, we are still not convinced that the benefits of LBC outweigh its cost. For this reason, CC should be the first choice for low-income developing countries.

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