

Liquid Compared With Conventional Cervical Cytology

A Systematic Review and Meta-analysis

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OBJECTIVE: To compare test performance characteristics of conventional Pap tests and liquid-based cervical cytology samples.

DATA SOURCES: Eligible studies, published between 1991 and 2007, were retrieved through PubMed/EmBase searching and completed by consultation of other sources.

METHODS OF STUDY SELECTION: Studies were selected if a conventional and a liquid-based sample were prepared from the same woman or when one or the other type of sample was taken from a separate but similar cohort. The current systematic review and meta-analysis is restricted to studies where all subjects were submitted to gold standard verification, based on colposcopy and histology of colposcopy-targeted biopsies, allowing computation of absolute and relative test validity

for cervical intraepithelial neoplasia grade 2 or worse. Randomized trials were selected as well if all test-positive cases were verified with the same gold standard, allowing computation of the relative sensitivity. Impact of study characteristics on accuracy was assessed by subgroup meta-analyses, meta-regression, and summary receiver operating characteristic curve regression.

TABULATION, INTEGRATION, AND RESULTS: The relative sensitivity, pooled from eight studies, with complete gold standard verification and from one randomized clinical trial, did not differ significantly from unity. Also, the specificity, considering high-grade and low-grade squamous intraepithelial lesions as cutoff, was similar in conventional and liquid cytology. However, a lower pooled specificity was found for liquid-based cytology when presence of atypical squamous cells of undetermined significance was the cutoff (ratio 0.91, 95% confidence interval 0.84–0.98). Differences in study characteristics did not explain interstudy heterogeneity.

CONCLUSION: Liquid-based cervical cytology is neither more sensitive nor more specific for detection of high-grade cervical intraepithelial neoplasia compared with the conventional Pap test.

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See related editorial on page 2.

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Liquid-based cytology is an alternative technique for transferring the cellular material collected with a spatula or a brush from the transformation zone of the uterine cervix. Unlike the conventional Pap test, the cells are not spread directly onto a slide but are transferred into a vial containing a fixative liquid. This container is then sent to a specially equipped laboratory. Currently, two commercially available liquid-based cytology systems, ThinPrep (Cytec Corporation, Boxborough, MA) and SurePath (formerly, AutoCyte PREP or CytoRich, TriPath Imaging Inc., Burlington, NC) are approved by the U.S. Food and Drug Administration and are allowed to claim increased cytologic detection of squamous intraepithelial lesions



Table 1. Study Characteristics of Included Studies

Author	Country	Study Population	Study Design	Study Size
Ferenczy, 1996	Canada, U.S.	Women referred for colposcopy	Concomitant testing, split-sample	364
Bergeron, 2001	France	Women referred for cone biopsy	Concomitant testing, direct-to-vial	500
Coste, 2003	France	1) Women referred for colposcopy 2) Screening population	Concomitant testing, split-sample	2,585 (828+1,757)
Confortini, 2004	Italy	Women referred for colposcopy; LBC was taken just before colposcopy, 30–60 days after abnormal CP	Concomitant testing, direct-to-vial	297
Confortini, 2005	Italy, Spain	Women referred for colposcopy; LBC just before colposcopy, 30–60 days after an abnormal CP	Concomitant testing, direct-to-vial	151
Hussein, 2005	U.K.	Follow-up of screen-positive women	Concomitant testing, split-sample	441
Longatto Filho, 2005	Brazil	Follow-up of screen-positive women (VIA, Pap test)	Concomitant testing, split-sample	1,095
Taylor, 2006	South-Africa	High-risk population, included in a see-and-treat trial (15% treated with cryotherapy)	Two-cohort, LBC and CP rotated every 6 months	LBC: 3,184C P: 2,463
Ronco, 2007	Italy	Women invited for screening	RCT	LBC-HC2: 22,708C P: 22,466

LBC, liquid-based cytology; CP, conventional Pap test; LEEP, loop electrosurgical excision procedure; ECC, endocervical curettage; TN, true negative; EC brush, endocervical brush; CIN, cervical intraepithelial neoplasia; HSIL, high-grade intraepithelial lesion; LSIL, low-grade intraepithelial lesion; VIA, visual inspection after application of acetic acid; RCT, randomized controlled trial; HC2, Hybrid Capture-2 assay (Digene Corporation, Gaithersburg, MD); HPV, human papillomavirus.

* Longatto Filho et al, 2005: Authors report that CP and LBC were interpreted blindly, but the same cytologists interpreted the two preparations from the same patient.

† Taylor et al, 2006: Cytology and colposcopy/histology were blinded to each other, but given study design with CP and LBC performed in separate periods, blinding cannot be considered as complete.

and a reduction in the number of unsatisfactory Pap tests compared with the conventional Pap.^{1,2}

Several systematic reviews regarding the performance of liquid-based cytology in detecting cervical cancer precursors have been performed over the last 7 years.^{3–19} Conclusions formulated by the reviewing authors have been disparate. Studies comparing test positivity rates for low-grade cytologic abnormalities often yielded more favorable results for liquid-based cytology,^{4,6,9,14} whereas in studies focusing on accuracy for biopsy-confirmed cervical intraepithelial neoplasia (CIN), no significant differences between the conventional Pap and liquid-based cytology have been found.^{10,12,19}

In this review, we synthesize available evidence from studies, where all tested subjects were submitted

to gold standard verification with colposcopy and biopsies if indicated, allowing unbiased assessment of the accuracy of conventional Pap and liquid-based cytology for histologically confirmed CIN following established guidelines for systematic review of observational studies and diagnostic research.^{20,21}

SOURCES

Eligible studies were retrieved through a PubMed-MEDLINE and EmBase search using the following key words: “cervix neoplasm,” “cervical intraepithelial neoplasia,” “cervix dysplasia” in combination with “monolayer,” “thin layer,” “liquid-based,” “Thin-Prep,” “CytoRich,” “Autocyte,” or “SurePath,” for the period January 1991 to May 2007. Additional papers were searched from the table of contents of five



LBC Procedure	Collection Method	Gold Standard	Independence LBC/CP Interpretation	Blinding Gold Standard Towards Type of Cytology
TP-beta	Acellon Combi sampler	Colposcopy on all; punch biopsy or LEEP and ECC for all cases	Blinded	Blinded
AutoCyte	Cervex-Brush	Colposcopy and cone biopsies for all subjects	Blinded	Blinded
TP2000	Not documented	Colposcopy on all subjects; biopsies if colposcopically positive	Blinded	Blinded
TP2000	Not documented	Colposcopy on all; histology of punch or excision biopsies, negative colposcopy accepted as TN	Blinded	Blinded
CellSlide	Spatula and EC brush	Colposcopy on all; histology documented for 22 CIN2+ cases	Blinded	Blinded
TP2000	Broom	Colposcopy on all; biopsy (punch or excision) if suspicion of HSIL (all) or LSIL (partial)	Not documented	Not documented
DNA-Citoliq	CP: Ayre spatula and EC brush LBC: EC brush.	Colposcopy on all, biopsies taken when indicated; conization and hysterectomy were taken into account	Blinded*	Blinded
TP2000	Spatula and EC brush	Colposcopy on all; ECC and biopsy of colposcopic abnormalities	Not of application, because of two-cohort design	Blinded†
TP2000	Plastic spatula and EC brush	Colposcopy depending on age, HPV test result, and study site; biopsies if colposcopic suspicion	Not of application, because RCT	Not blinded, quality review of CIN cases was blinded

gynecologic journals (*American Journal of Obstetrics and Gynecology*; *Gynecologic Oncology*, *Journal of Reproductive Medicine*, *Journal of Lower Genital Tract Disease*, and *Obstetrics & Gynecology*) and four cytopathology journals (*Acta Cytologica*, *Cancer Cytopathology*, *Cytopathology and Diagnostic Cytopathology*). Moreover, a systematic hand-search was performed on the reference lists of retrieved studies. No language restriction was applied. Authors were contacted for provision of additional data where needed.

STUDY SELECTION

Two types of study design were distinguished: 1) concomitant testing design and 2) two-cohort design. In the concomitant testing design, two cervical cell samples are prepared from the same patient. Most often a single sample is taken from the uterine cervix, a conventional Pap is prepared, and the residual cellular material remnant on the sampling device is then transferred into a vial with fixative liquid (“split-sample”). Occasionally, two separate samples are collected: one for the conventional Pap and another

one for liquid-based cytology. In the two-cohort design, conventional Pap samples and liquid-based cytology samples are taken from women belonging to separate but similar populations.

The current review is restricted to studies where all subjects were submitted to gold standard verification, based on colposcopy and histology of colposcopy-targeted biopsies, allowing evaluation of the absolute and relative test validity without verification bias for cervical intraepithelial neoplasia grade 2 (CIN 2+) or worse. Randomized controlled studies with at least 90% completeness in follow-up confirmation of cytologically positive women were added to the meta-analysis of the relative sensitivity. This addition is justified because, in randomized controlled trials, the ratio of the detection rate of CIN 2+ in the liquid-based cytology arm over that in the conventional Pap arm is equivalent to the ratio of the absolute sensitivities derived from studies with complete gold standard verification.²²

Two independent reviewers assessed eligibility of studies and extracted data from selected reports. In



case of discordance, differences were discussed until consensus was reached.²³

The 1991 version of The Bethesda Reporting System was used for the cytologic classification of the test result.²⁴ We considered three threshold levels for positive cytology: atypical squamous cells of undetermined significance or worse (ASC-US+), low-grade squamous intraepithelial lesions or worse (LSIL+), and high-grade squamous intraepithelial lesions or worse (HSIL+). Atypical glandular lesions were assimilated together within the ASC-US category and adenocarcinoma in situ/adenocarcinoma together with HSIL+. Categories of cytologic abnormality, defined according to other reporting formats, were converted into The Bethesda Reporting System using published standard translation tables.²⁵ We used the CIN nomenclature to describe histologic outcomes.²⁶

Study characteristics potentially influencing test validity estimation were derived from the Standards for Reporting of Diagnostic Accuracy.²⁷ The following study quality properties and population characteristics were checked and summarized in comprehensive tables: commercial liquid-based cytology system; service properties (geographical area, type of health service, professional groups taking the smears); clinical setting (screening population, women examined for clinical indications, or mixed population); inclusion and exclusion criteria; age range; blinding of interpreters to results from the same subject; applied quality system to assure reliability of the test and outcome result (selective or systematic rereading of cytologic and histologic samples by expert cytologists or cytopathologists); collection device used to sample cervical cells; and the level of experience of cytotechnologists in liquid-based cytology.

The absolute and relative sensitivity and specificity for the detection of CIN 2+ were pooled for different levels of test positivity. For computation of ratios, parameters of liquid-based cytology always were put in the numerator and those for conventional Pap in the denominator.

Forest plots were constructed using meta-analytical models to pool ratios of proportions.²⁸ Interstudy heterogeneity was assessed with Cochran's *Q* test, and the percentage of total variation across studies due to heterogeneity was evaluated by the *I*² measure.^{29,30} Random effect models were used for pooling when the *P* value corresponding with Cochran's *Q* test was less than .20; otherwise, fixed-effect models were used, where each individual study was weighted with the reciprocal of its variance.^{31,32}

To estimate the pooled absolute sensitivity, specificity, and the diagnostic odds ratio, we used hierarchical summary receiver operating characteristic regression, which incorporates the intrinsic negative correlation between the log odds of true- and false-positivity rates and allows for sparse data.³³⁻³⁵

The potential influence of study characteristics and technical covariates on interstudy heterogeneity of sensitivity and specificity was explored using subgroup meta-analyses and meta-regression.³⁶⁻³⁸ The impact of covariates on the diagnostic odds ratio (OR) was assessed by summary receiver operating characteristics regression.³⁹ Diagnostic OR was defined as the ratio of the sensitivity odds over the odds of 1-specificity.

RESULTS

We retrieved 126 reports from 109 studies that described test positivity and/or adequacy rates in both conventional Pap and liquid-based cytology.²³ In 60 studies, the concomitant testing design was applied, but in only seven were all cytologic results verified with the standard reference test.⁴⁰⁻⁴⁶ Four selected studies used split samples.^{40,42,45,46} In one study, two samples were taken from each woman, and the order (liquid-based cytology first or second) was randomized.⁴¹ The two studies of Confortini et al^{43,44} included women in whom a prior conventional Pap was compared with a liquid-based cytology taken 30–60 days later just before a colposcopy examination.

Among the 49 two-cohort studies, only one was found in which the choice of preparation method was rotated every 6 months and where all women were submitted to gold standard verification.⁴⁷ Among the two retrieved randomized trials,^{48,49} only the Italian one⁴⁹ was selected for inclusion into the meta-analysis of the relative sensitivity. The Swiss trial was excluded because of insufficient completeness of verification of test positives: less than 70% for HSIL cases and no verification data for abnormalities of lower severity.⁴⁸

The evaluated liquid-based cytology systems were as follows: ThinPrep (n=6), AutoCyte (n=1), DNA Citoliq System (n=1) (Digene Brazil Inc., Sao Paulo, Brazil), and CellSlide (Menarini Diagnostics, Firenze, Italy) (n=1). Most studies involved women referred because of previous cervical abnormalities. Nevertheless, one split-sample study included a screening population,⁴² and also the randomized Italian trial⁴⁹ was nested in an organized screening system. Nonpublished data necessary for the computation of the relative sensitivity at cutoff HSIL+ in the Italian trial were requested and received directly from the author.



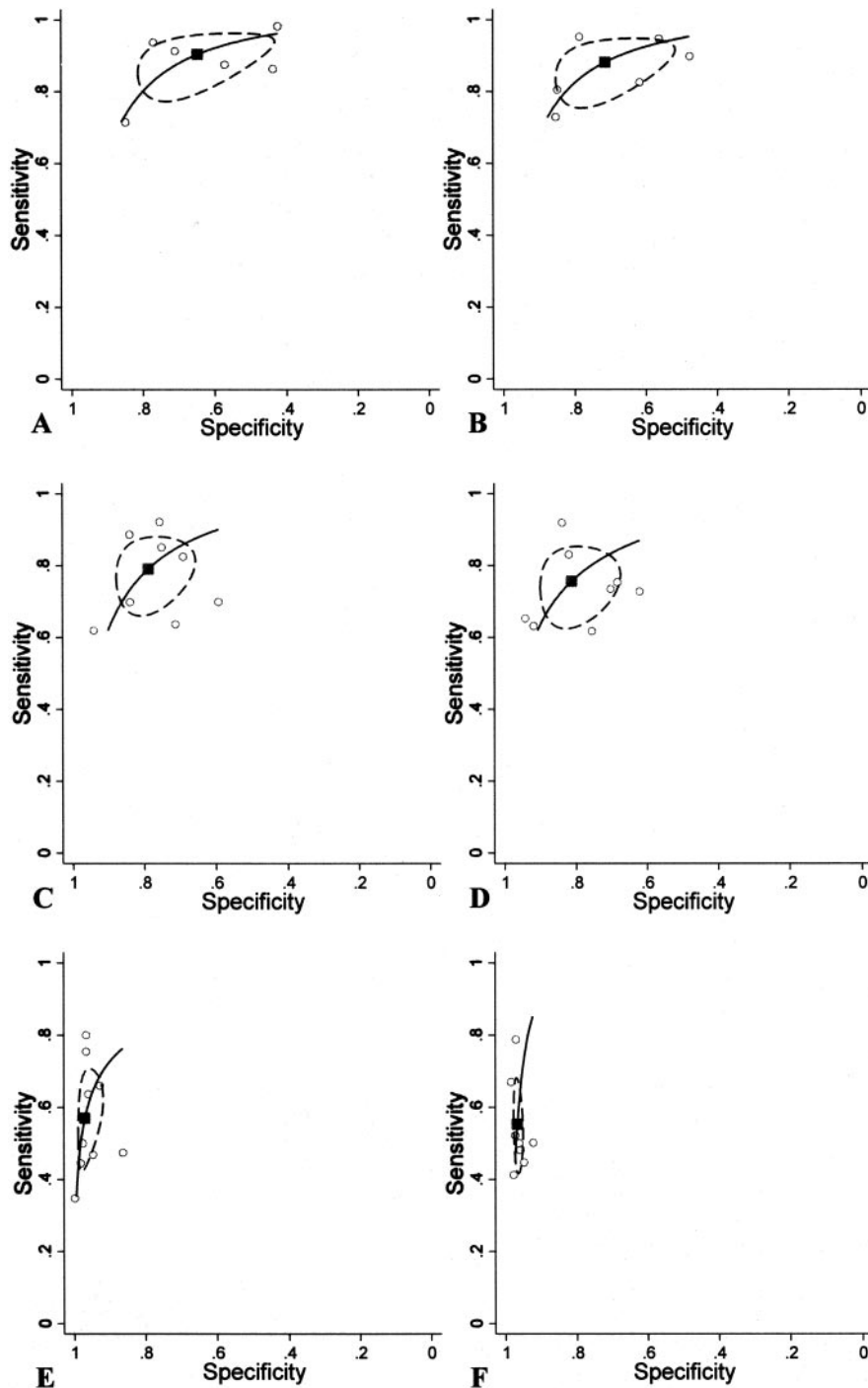


Fig. 1. Hierarchical summary receiver operating characteristic curves displaying the fitted joint variation of sensitivity and specificity of liquid (A, C, E) and conventional cytology (B, D, F) at cutoff high-grade squamous intraepithelial lesion or worse (A, B), at cutoff low-grade squamous intraepithelial lesion or worse (B, C), and at cutoff atypical squamous cells of undetermined significance or worse (E, F) for detection of underlying cervical intraepithelial neoplasia 2 or worse in eight studies with complete gold standard verification. The dots represent the observed sensitivity and specificity in individual studies. The square corresponds to the pooled sensitivity and specificity, and the area surrounded by an interrupted line corresponds to the 95% confidence ellipse.

Arbyn. Liquid Compared With Conventional Cervical Cytology. *Obstet Gynecol* 2008.

Other study characteristics are summarized in Table 1. The number of 25 quality issues of the Standards for Reporting of Diagnostic Accuracy guideline, which were appropriately addressed in the published reports, varied from 14 to 22 (data not shown).

The joint distribution of the sensitivity and specificity (derived from studies with complete gold stan-

dard verification) of liquid-based cytology and conventional Pap for underlying CIN 2+ and the corresponding summary receiver operating characteristic curves are displayed in Figure 1. The values of the pooled sensitivity, specificity, and diagnostic odds ratio are shown in Table 2. The two studies of Confortini et al^{43,44} were excluded from the meta-



Table 2. Meta-Analysis: Pooled Absolute Sensitivity, Specificity and Diagnostic Odds Ratio of Liquid-Based Conventional Cytology at Three Cytologic Cutoffs for Cervical Intraepithelial Neoplasia 2 or Worse, Estimated by Hierarchical Summary Receiver Operating Characteristic Regression

	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Diagnostic OR (95% CI)
Liquid-based cytology			
HSIL+	57.1 (46.3–67.2)	97.0 (93.8–98.6)	42.9 (20.6–89.2)
LSIL+	79.1 (70.1–86.0)	78.8 (69.8–85.7)	14.1 (7.7–25.7)
ASC-US+	90.4 (82.5–95.0)	64.6 (50.1–76.8)	17.3 (8.9–33.5)
Conventional cytology			
HSIL+	55.2 (45.5–64.7)	96.7 (95.6–97.5)	36.2 (21.2–61.9)
LSIL+	75.6 (66.5–83.0)	81.2 (71.9–88.0)	13.4 (7.1–25.4)
ASC-US+	88.2 (80.2–93.2)	71.3 (58.3–81.6)	18.5 (9.8–35.0)

CI, confidence interval; OR, odds ratio; HSIL+, high-grade squamous intraepithelial lesion or worse; LSIL+, low-grade squamous intraepithelial lesion or worse; ASC-US+, atypical squamous lesion of undetermined significance or worse.

analyses with ASC-US as cutoff because all included women had at least an equivocal conventional Pap test. The pooled sensitivity varied substantially by cytologic cutoff (respectively, 57.1%, 95% confidence interval [CI] 46.3–67.2%, 79.1%, 95% CI 70.1–86.0%, 90.4%, 95% CI 82.5–95.0%, for liquid-based cytology at, respectively, HSIL+, LSIL+, and ASC-US+). The pooled sensitivities for conventional Pap were not significantly lower. The specificity of liquid-based cytology dropped by decreasing cutoff: 97.0% (95% CI 93.8–98.6%) at HSIL+, 78.8% (95% CI 69.8–85.7%) at LSIL+, and 64.6% (95% CI 50.1–76.8%) at ASC-US+.

The specificities of conventional Pap at cutoff HSIL+ and LSIL+ were in the same range as liquid-based cytology. However, at cutoff ASC-US+, the specificity of conventional Pap was higher (71% compared with 65%). The diagnostic odds ratios were similar for conventional and liquid-based preparations.

In Table 3, we summarize the relative sensitivity and specificity for CIN 2+ pooled from nine studies, separated by cytologic cutoff. The variation of the accuracy ratios, considered at cutoff HSIL or worse and ASC-US or worse, is illustrated in Figure 2. Overall, liquid-based cytology was minimally, but not

significantly, more sensitive in detecting underlying CIN 2+ than conventional Pap (ratios between 1.02 and 1.05, depending on the cytologic cutoff). Two individual studies showed a significantly higher sensitivity at cutoff HSIL or LSIL^{43,45} and one other at cutoff ASC-US.⁴⁶ The specificities of liquid-based cytology and conventional Pap did not differ from each other at cutoff HSIL+ or LSIL+, but liquid-based cytology was statistically significantly less specific at cutoff ASC-US+ (ratio 0.91, 95% CI 0.84–0.98). The relative sensitivities at cutoffs HSIL+, LSIL+, and ASC-US+ for the outcome of CIN 2+ derived from the Italian randomized controlled trial⁴⁹ were 1.07 (95% CI 0.71–1.26), 1.03 (95% CI 0.74–1.43), and 1.17 (95% CI 0.87–1.56), respectively. These values were all included within the confidence intervals around the respective pooled values.

The variation in relative sensitivity and specificity for CIN 2+, defined at cutoff HSIL+, pooled by subgroups, is shown in Table 4. Between-group heterogeneity in relative sensitivity never was statistically significant. However, for relative specificity, there was significant heterogeneity between groups due to study design and liquid-based cytology system. This heterogeneity in relative specificity always was due to one

Table 3. Ratio of Sensitivity and Specificity for Cervical Intraepithelial Neoplasia 2 or Worse of Liquid-Based Relative to Conventional Cytology, Pooled from Nine Studies*

Test Threshold	Relative Sensitivity			Relative Specificity		
	Pooled Estimate (95% CI)	No. of Studies	P	Pooled Estimate (95% CI)	No. of Studies	P
HSIL+	1.05 (0.95–1.16)	9	.109	0.99 (0.98–1.01)	8	.001
LSIL+	1.03 (0.96–1.11)	9	.027	0.97 (0.94–1.01)	8	<.001
ASC-US+	1.03 (0.97–1.09)	7	.002	0.91 (0.84–0.98)	6	<.001

CI, confidence interval; HSIL+, high-grade squamous intraepithelial lesion or worse; LSIL+, low-grade squamous intraepithelial lesion or worse; ASC-US+, atypical squamous lesion of undetermined significance or worse.

* Eight studies with complete verification by colposcopy and/or biopsy and one study by randomized controlled trial.



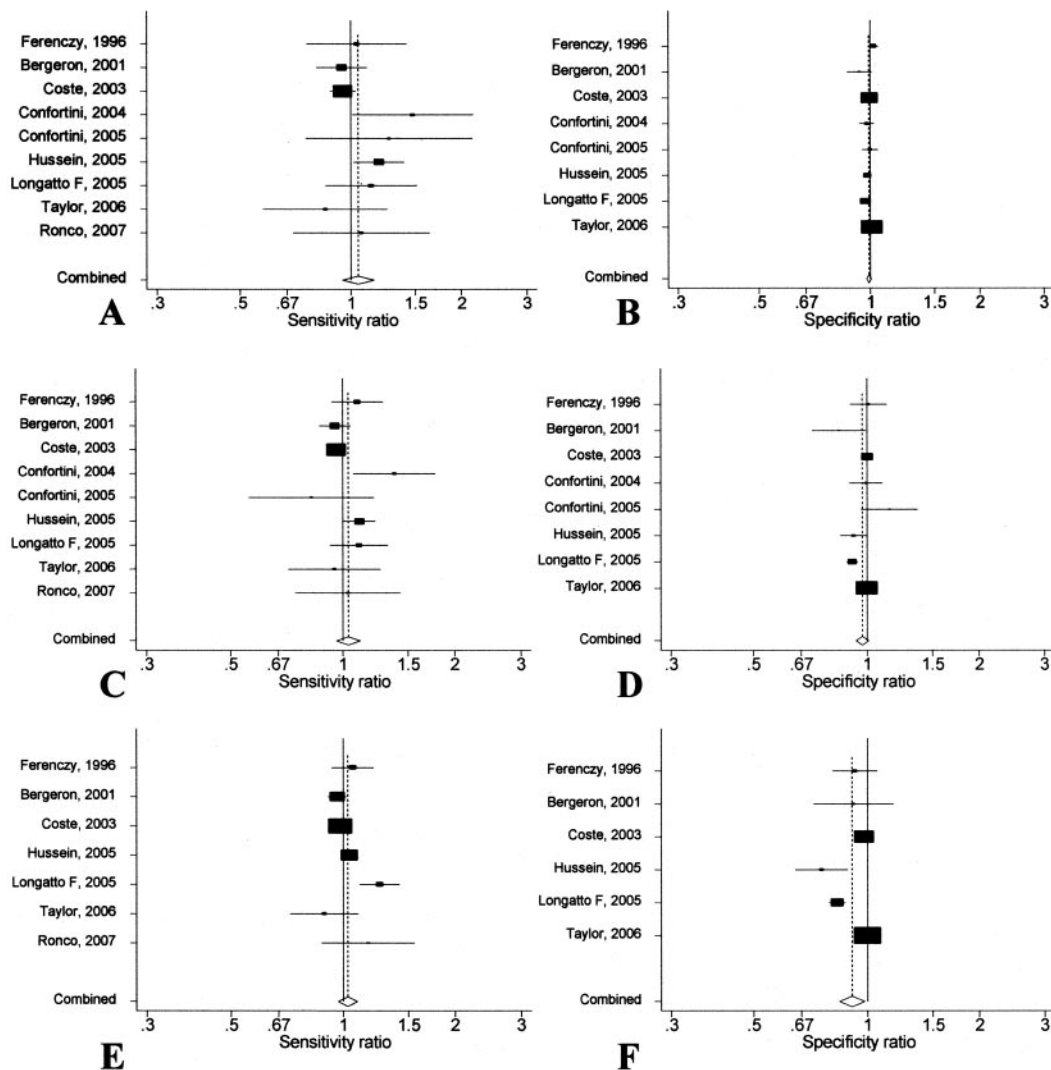


Fig. 2. **A.** Relative sensitivity at cutoff high-grade squamous intraepithelial lesion or worse (HSIL+). **B.** Relative specificity at cutoff HSIL+. **C.** Relative sensitivity at cutoff low-grade squamous intraepithelial lesion or worse (LSIL+). **D.** Relative specificity at cutoff LSIL+. **E.** Relative sensitivity at cutoff atypical squamous cells of undetermined significance or worse (ASC-US+). **F.** Relative specificity at cutoff ASC-US+ to detect high-grade cervical intraepithelial neoplasia 2 or worse of liquid-based compared with conventional cytology.

Arbyn. Liquid Compared With Conventional Cervical Cytology. Obstet Gynecol 2008.

study: higher specificity ratio in the two-cohort study (1.01, 95% CI 1.00–1.02)⁴⁷ and lower specificity ratio with the DNA Citoliq system (0.97, 95% CI 0.95–0.99).⁴⁶ None of the other study characteristics contributed in explaining interstudy variation of the test accuracy.

No significant differences were found at cutoff LSIL+, but at cutoff ASC-US+, DNA Citoliq showed a higher sensitivity ratio (1.25, 95% CI 1.11–1.42) but also a lower specificity ratio (0.83, 95% CI 0.79–0.87).⁴⁶ Summary receiver operating characteristics regression, using ThinPrep as reference, identified a

lower diagnostic OR for AutoCyte at cutoff HSIL+. The contrast in diagnostic OR between conventional and liquid-based cytology was not influenced by the number of quality issues of the Standards for Reporting of Diagnostic Accuracy guideline addressed in the individual reports ($P=.84$, $P=.37$, and $P=.65$ for cutoffs HSIL+, LSIL+, and ASC-US+, respectively).

CONCLUSION

Only seven studies used the protocol recommended for the evaluation of diagnostic tests, which consists in applying two or more tests to the same subjects and verifying all



Table 4. Subgroup Meta-Analyses: Variation of Relative Accuracy of Liquid Compared With Conventional Cytology* According to Study Characteristics

	Pooled Sensitivity Ratio (95% CI)	No. of Studies	<i>P</i> [†]	Pooled Specificity Ratio (95% CI)	No. of Studies	<i>P</i> [†]
Clinical setting			.784			.792
Screening [‡]	1.03 (0.76–1.40)	2	.821	1.00 (0.99–1.00)	1	–
Follow-up/high risk [‡]	1.05 (0.94–1.17)	8	.063	0.99 (0.97–1.01)	8	.001
Study design			.742			.001
Concomitant testing	1.07 (0.95–1.20)	7	.053	0.99 (0.97–1.00)	7	.052
Two-cohort/RCT	0.94 (0.71–1.26)	2	.421	1.01 (1.00–1.02)	1	–
Split sample/direct-to-vial			.999			.999
Split-sample	1.06 (0.92–1.22)	4	.065	1.00 (0.98–1.01)	3	.190
Direct-to-vial	1.05 (0.87–1.27)	5	.195	0.98 (0.96–1.01)	5	<.001
Gold standard			.876			.999
Colposcopy and histology if indicated	1.07 (0.60–1.64)	1	–	–	0	–
Complete colposcopy, histology if indicated	1.10 (0.94–1.28)	6	.027	0.99 (0.98–1.01)	6	.001
Complete histology	0.96 (0.84–1.11)	2	.601	0.98 (0.89–1.08)	2	.021
LBC system			.405			.001
ThinPrep	1.07 (0.92–1.23)	6	.047	1.00 (0.99–1.01)	5	.053
AutoCyte	0.95 (0.81–1.11)	1	–	0.94 (0.87–1.01)	1	–
CellSlide	1.27 (0.75–2.15)	1	–	1.00 (0.95–1.05)	1	–
DNA-Citoliq	1.14 (0.85–0.51)	1	–	0.97 (0.95–0.99)	1	–

CI, confidence interval; RCT, randomized controlled trial; LBC, liquid-based cytology.

* At cutoff high-grade squamous intraepithelial lesion or worse for cervical intraepithelial neoplasia 2 or worse.

[†] *P* corresponding with test for interstudy heterogeneity; bold type indicates between-group heterogeneity.

[‡] Study of Coste et al, 2003, contributed a screening group and a follow-up group.

with a valid gold standard.^{27,50} One two-cohort study could be added to the meta-analysis, because all subjects belonging to similar and contemporary cohorts were verified with the same gold standard.⁴⁷ We identified two studies,^{48,49} where women were randomized to conventional Pap or liquid-based cytology, but only the Italian trial⁴⁹ was sufficiently empowered and provided colposcopy and or biopsy outcomes for nearly all the screen-positives needing referral.

Pooling of the studies with complete verification did not reveal any statistically significant difference in sensitivity or specificity between liquid-based cytology and conventional Pap, with the exception of a lower specificity of liquid-based cytology at cutoff ASC-US.

Because of the limited number of studies with complete confirmatory testing, we included also studies with incomplete verification (Arbyn M, Delvenne P, Bourgain C, Bergeron C, Klinkhamer PJ, Bulten J. Comparison of test performance of liquid-based versus conventional Pap smears to detect cervical cancer precursors [abstract]. 13th Cochrane Colloquium, Melbourne, Australia, October 22–26, 2005).²³ We restricted inclusion to studies with confirmation for at least 80% of positive results and 5% of cases with a normal cytology result. Assuming that verification of cytologic cases was random, we could compute accuracy measures adjusted for verification using bootstrapping for estimation of the standard errors.^{51–53} Again, no statisti-

cally significant difference in sensitivity or specificity for CIN 2+ between liquid-based cytology and conventional Pap was observed (data not shown).

Concerns have been raised with respect to a potential disadvantage for liquid-based cytology when the collected cells are first used to prepare a conventional Pap and the residual material is used for liquid-based cytology. It might be possible that diagnostic elements are transferred to the conventional slide that are not available for the liquid-based cytology.^{8,15} The observation of higher rates of HSIL in liquid-based cytology compared with conventional Pap in two-cohort studies and the finding of similar HSIL rates in conventional Pap and liquid-based cytology in studies based on concomitant testing with split-samples could be interpreted as corroborating this hypothesis.²³ In the five trials included in our meta-analysis in which separate samples were taken,^{41,43,44,47,49} however, better sensitivity for CIN 2+ was not found. Moreover, subgroup meta-analyses showed that the relative sensitivity, stratified by cytologic category, was similar over the different study designs, including a large randomized screening trial.

The quality of study design and completeness of reporting of study characteristics, assessed according to the Standards for Reporting of Diagnostic Accuracy guidelines, did not modify the conclusions of our meta-analyses. However, the fact that the number of items in the Standards for Reporting of Diagnostic



Accuracy guidelines that were appropriately addressed in the individual studies did not modify accuracy does not allow the conclusion that study quality does not matter. We only included studies with a robust design. A previous review, evaluating the relation between study quality and test-positivity rates, found a negative association between the ratio of HSIL rates in liquid-based cytology compared with conventional Pap and study quality.¹⁹

The choice of the liquid-based cytology system contributed to some degree in explaining part of interstudy heterogeneity. DNA Citoliq showed higher sensitivity and lower specificity than conventional Pap, but the diagnostic ORs were not significantly different.⁴⁶ AutoCyte was (nonsignificantly) less sensitive and specific than conventional Pap at cutoff HSIL, but this resulted in a significantly lower diagnostic OR.⁴¹ However, if unsatisfactory preparations of women with CIN 2+ were considered as false-negative cases—as was done by the author—then the diagnostic OR of AutoCyte became higher (but not significantly) than that of conventional Pap.

From a previous systematic review of two-cohort studies, we concluded that liquid-based cytology results in fewer unsatisfactory samples and that the average duration of microscopic interpretation is reduced by about 30%.²³ The substantial reduction in the number of inadequate samples, observed in the United Kingdom pilot studies (from 9–10% to 1–2%), tipped cost-effectiveness analyses in favor of liquid-based cytology and convinced the National Health Service to opt for liquid-based cytology as the preferred screening technique.^{54,55} However, this apparent economic advantage might be peculiar to the United Kingdom where inadequacy rates for the conventional Pap were excessively high.⁵⁶

Cytotechnologists and pathologists consistently prefer liquid-based cytology because microscopic interpretation is facilitated by the uniform spread of epithelial cells in a thin layer.^{18,54,57} Another advantage is that additional investigations can be performed on the fluid remnant after cytologic examination, such as testing for high-risk human papillomavirus types to triage women with equivocal Pap results.^{58–61} Finally, a thin-layer specimen might be more appropriate for automated screening devices.⁶²

Liquid-based cytology is more costly in terms of capital investment, operating costs, and disposables. In most countries, the proportion of unsatisfactory conventional smears is lower than 3%. Therefore, using liquid-based cytology will not result in a substantial reduction in recalls for unsatisfactory samples. On the contrary, higher rates of equivocal or mild

abnormalities will increase follow-up costs and shift resources from activities targeting those women who are at highest risk.^{63,64}

In 2007, only eight studies and one well-conducted randomized trial are available that allow unbiased evaluation of the accuracy of liquid-based cytology for histologically confirmed CIN 2 or worse. Pooling of these studies indicated that liquid-based cytology is neither more sensitive nor more specific than conventional Pap and these findings were rather consistent over study design, clinical settings, and liquid-based cytology systems.

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