Comparison of Liquid-Based Cytology With Conventional Cytology for Detection of Cervical Cancer Precursors

A Randomized Controlled Trial

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Context Liquid-based cytology has been developed as an alternative for conventional cervical cytology. Despite numerous studies and systematic reviews, controversy remains about its diagnostic accuracy.

Objective To assess the performance of liquid-based cytology compared with conventional cytology in terms of detection of histologically confirmed cervical intraepithelial neoplasia (CIN).

Design, Setting, and Participants Cluster randomized controlled trial involving 89 784 women aged 30 to 60 years participating in the Dutch cervical screening program at 246 family practices. One hundred twenty-two practices were assigned to use liquid-based cytology and screened 49 222 patients and 124 practices were assigned to use the conventional Papanicolaou (Pap) test and screened 40 562 patients between April 2004 and July 1, 2006. Patients were followed up for 18 months through January 31, 2008.

Intervention Screening for CIN using liquid-based cytology or conventional papanicolaou (Pap) test and the blinded review of all follow-up of screen-positive women (blinded to the type of cytology and the initial result).

Main Outcome Measures Intention-to-treat and per-protocol analysis of the detection rates of and positive predictive values for histologically verified CIN in both cytology systems. Outcomes are presented as crude and adjusted rate ratios (adjustment for age, urbanization, study site, and period).

Results The adjusted detection rate ratios for CIN grade 1+ was 1.01 (95% confidence interval [CI], 0.85-1.19); for CIN grade 2+, 1.00 (95% CI, 0.84-1.20); for CIN grade 3+, 1.05 (95% CI, 0.86-1.29); and for carcinoma, 1.69 (95% CI, 0.96-2.99). The adjusted positive predictive value (PPV) ratios, considered at several cytological cutoffs and for various outcomes of CIN did not differ significantly from unity.

Conclusion This study indicates that liquid-based cytology does not perform better than conventional Pap tests in terms of relative sensitivity and PPV for detection of cervical cancer precursors.

Trial Registration trialregister.nl Identifier: NTR1032

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THE CONVENTIONAL PAPANICOlaou (Pap) test is considered suboptimal due to false-negative and false-positive test results. This is caused by the poor quality of sampling and preparation (obscuration by blood or inflammation, bad cell fixation, and inhomogeneous distribution of cells) and by errors in detection and interpretation. Liquid-based cytology was developed as an alternative. For the liquid-based cytology, the cervical cells are collected with a traditional sampling device and rinsed into a vial with preservation solution rather than being smeared on a slide.[1-3] Because only a representative portion of the sample is used, the residual material in the vial may be used for ancillary testing such as reflex human papillomavirus (HPV) testing and other molecular tests.[3]

The accuracy of liquid-based cytology has been compared with conventional cytology in numerous studies with disparate results. Recent systematic reviews concluded that because of a lack of well-designed comparative studies, convincing evidence to determine the superiority of either method for detecting high-grade lesions does not exist.[4-7]

The objective of this prospective trial was to compare the screening perfor-

For editorial comment see p 1809.

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mance of the 2 screening methods in terms of test positivity rates, histological detection rates, and positive predictive values (PPVs). The liquid-based system that was used was ThinPrep (Hologic Corp, Marlborough, Massachusetts). The results of the cytology showing the differences in test positivity and specimen adequacy were recently published.[8] This article focuses on the histological detection rates and PPVs.

METHODS

This randomized controlled trial involved women aged 30 to 60 years who were participating in the Dutch cervical screening program. They are invited for a Pap test every 5 years. The sample is taken by the family physician. The NETHCON (Netherlands ThinPrep vs Conventional Cytology) trial was performed by 2 clinical laboratories (PAMM Laboratories, Eindhoven, and Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands) in collaboration with local gynecologists, pathologists, and family physicians. Ethical approval was obtained by the Dutch Ministry of Health, Welfare, and Sport. Informed refusal was offered with an information folder.

Family practices associated with the clinical study sites were randomly assigned to the liquid-based cytology or the conventional Pap test group. All women screened at 1 of the participating family practices were included in the study.

Screen-positive women were followed up prospectively for 18 months after the initial screening test. When available, histological follow-up was used as a reference standard. Abnormal cases without histological follow-up, mostly minor abnormalities, had an additional Pap test. The main outcomes were the ratios of the detection rates (DRs) of histologically confirmed cervical intraepithelial neoplasia (CIN) or cervical carcinoma between the diagnostic tests. The absolute test sensitivity cannot be assessed in a randomized controlled trial unless the reference standard is applied to all screened participants. However, the ratio of the DRs equals relative sensitivity. Because the prevalence of disease is equal in both groups due to randomization, the ratios of the PPVs reflect differences in specificity. Thus, the ratios of PPVs of CIN grade 1 or low-grade squamous intraepithelial lesion (SIL) or more severe (CIN grade 1+ or low-grade SIL+) or CIN grade 2 or high-grade SIL or more severe (CIN grade 2+ or high-grade SIL+), were secondary outcomes. The PPVs were based on cytologically or histologically confirmed outcomes.

The calculation of the sample size was documented previously[8] and was based on 0.6% detection of CIN grade 2+ using the conventional Pap test and an expected 33% increase using liquid-based cytology with an α of .05 and β of .20, an intraclass correlation coefficient of 0.05, an average cluster size of 250, and a standard deviation of 200. This resulted in a coefficient of variation of 0.8 and design effect of 1.59.[9] By multiplication of the design effect by sample size without cluster effect, a sample size of 44 947 women in each group was obtained.

Recruitment started in April 2003 and concluded in July 2006 after the enrollment of 89 960 women. One hundred seventy-six women were excluded from analysis because their family practice had not been randomized. Local pathology databases were used for data storage. Initial cytological results were linked with the cytological and histological follow-up outcomes assessed within an 18-month period. Follow-up data were retrieved from the local and national pathology databases, which contain the results of all examined specimens in the Netherlands.[10]

A cluster randomization was chosen for practical reasons and to prevent contamination by preference of patient or physician (selection bias). The family practices associated with the 2 study sites served as the units of randomization. Population areas, determined by postal code, with fewer than 100 000 residents were considered to be low-level urban areas and those with more than 100 000 were considered to be high-level urban areas. Subsequently, the family practices were allocated to either screening method using a binomial random number generator.[11] All practices were included in the randomization procedure and informed by mail on the results of the randomization. They all agreed with the outcome. Adherence of the family practices to their assignment was checked periodically.

To prevent selective assessment bias, study personnel—gynecologists, pathologists, cytotechnologists, and others—involved in the follow-up and review of histology and cytology were blinded to the cytology screening system used.

All family practices were informed about the study before the start of the trial and consented with participation. Practices assigned to the liquid-based cytology group received written instructions about sample collection and additional training, either by a regional course or by in-home instruction by the manufacturer. Sample taking was performed by the family physician or his/her assistant.

The Rovers Cervex-Brush (Rovers Medical Devices BV, Oss, the Netherlands) was used for sample taking in both study groups. The conventional Pap tests were prepared by spreading cells quickly on a glass slide and performing cell fixation within a few seconds. The liquid-based cytology samples were prepared by transferring the sampled cells from the brush to the transport solution by firmly rotating and pushing the brush against the vial wall 10 times. Liquid-based cytology samples were processed at the laboratory with the ThinPrep 3000 processor (Hologic Corp).[1,12]

The introduction phase for liquid-based cytology started with a 3-day training course for cytotechnologists and pathologists provided by the manufacturer. During the learning stage, a minimum of 200 liquid-based cytology slides were taken from the routine workload and screened. All slides were rescreened by another cytotechnologist. Primary

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screening was not allowed before passing a final test. A training course for the technical operators of the the processor was also provided. One study site had been using the liquid-based cytology slides for a year. The other study site had no prior experience with this screening method. Smears were screened and classified by cytotechnologists according to the CISOE-A classification system. This Dutch classification system can be easily translated into the Bethesda 1991 subcategories atypical squamous or glandular cells of undetermined significance (ASCUS/AGUS), low-grade SIL, and high-grade SIL.[12,13] Borderline and low-grade abnormalities were reviewed by a supervising cytotechnologist and high-grade abnormalities were reviewed by both a supervising cytotechnologist and cytopathologist. Cytological test results were categorized as within normal limits; ASCUS/AGUS; low-grade SIL; or high-grade SIL, squamous cell carcinoma, adenocarcinoma in situ, or cervical adenocarcinoma.

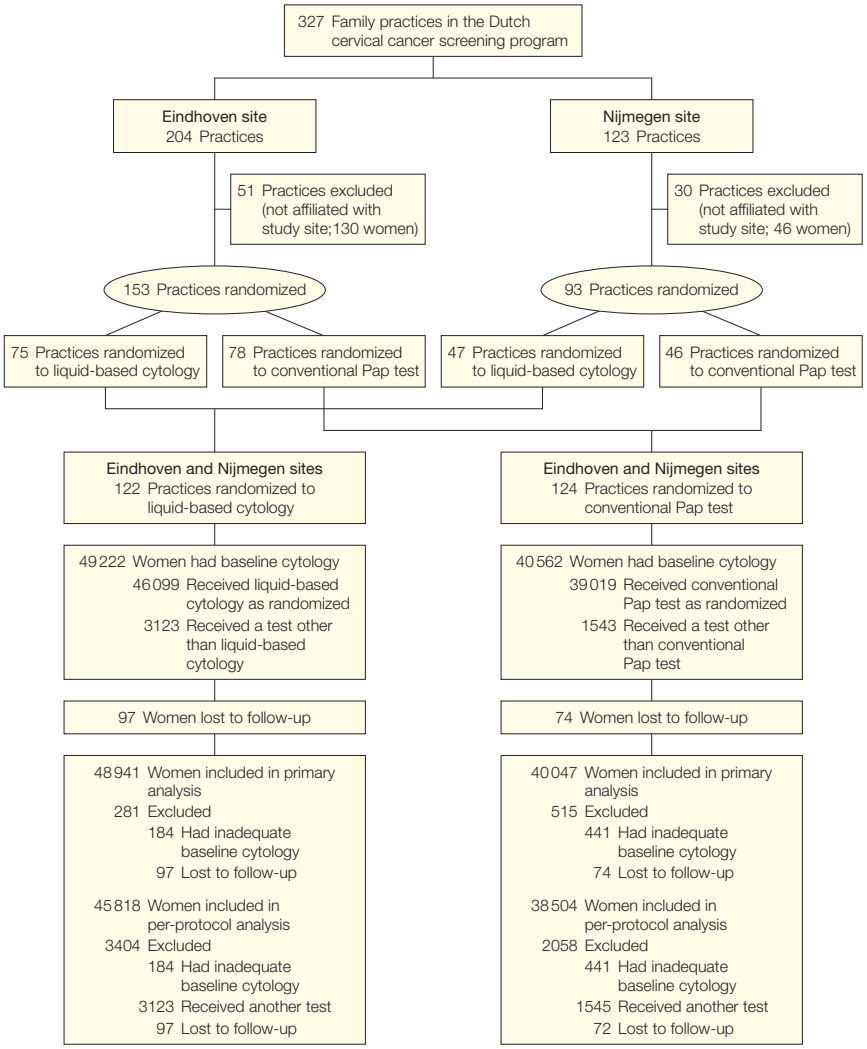
Screen-positive cases had follow-up tests in accordance with the guidelines of the Dutch Society of Pathologists and the Dutch Society of Obstetrics and Gynecology.[12] Follow-up tests included cytological testing, colposcopy, or histology. Women with equivocal or low-grade cytological abnormalities on the initial test were offered repeat cytology. When both the first test (at 6 months) and the second test (at 18 months) returned with normal results, the patient was referred back to the screening program. Women whose initial abnormality is found to persist or progress in the first or second repeat test are advised to visit a gynecologist for colposcopy. Histology is taken from colposcopically abnormal areas. High-grade cytological abnormalities on initial or repeat test are immediately referred to a gynecologist for colposcopy and further histological evaluation.

Family practices received a reminder when follow-up tests are not performed within a previously defined time frame, according to routine national procedures.

Assessment of the primary final outcome was based on blinded review of all histological follow-up. The secondary final outcome was also based on reviewed histological follow-up, but in cases for which no histological follow-up existed, this outcome was based on blinded review of follow-up cytology.

Cervical histology was blindly reviewed in all test-positive cases for which histology was performed within 18 months. The most severe diagnosis was registered when more histological specimens were available in the follow-up period. When no histology was available within 18 months, the most severe cytology was reviewed and used for assessment of the secondary outcome. A panel of 4 experienced pathologists who were blinded to the cytological system, the original cytological and histological findings, and all follow-up data reviewed the histology. Experienced cytotechnologists reviewed cytology, using the same protocol. Discrepancy or concordance between the original diagnosis and review diagnosis was assessed using 4 classes: within normal limits; atypia or CIN grade 1 and their glandular equivalents for histology and ASCUS/AGUS or low-grade SIL

Figure. Participant Flow of Enrollment and Allocation in the Trial



Pap indicates Papanicolaou.

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Table 1. Population Characteristics

Variable	Total No. of Women	No. (%) of Women: Liquid-Based Cytology	No. (%) of Women: Conventional Papanicolaou Test
Study site			
Eindhoven	57 045	32 888 (57.6)	24 157 (42.4)[a]
Nijmegen	32 739	16 334 (49.9)	16 405 (50.1)
Urbanization			
High	30 721	17 242 (56.1)	13 479 (43.9)[a]
Low	59 063	31 980 (54.2)	27 083 (45.9)
Age, y			
<30	571	325 (56.9)	246 (43.1)
30-34	18 597	10 364 (55.7)	8233 (44.3)
35-39	12 906	7233 (56.0)	5673 (44.0)
40-44	16 140	8959 (55.5)	7181 (44.5)
45-49	10 845	5935 (54.7)	4910 (45.3)[a]
50-54	11 633	6183 (53.1)	5450 (46.9)
55-59	16 300	8698 (53.4)	7602 (46.6)
>59	2792	1525 (54.6)	1267 (45.4)
Study period			
1	44 813	24 250 (54.1)	20 563 (45.9)[a]
2	44 971	24 972 (55.5)	19 999 (44.5)
No. of cases in intention-to-treat analysis	89 784	49 222 (54.8)	40 562 (45.2)
No. of cases in per-protocol analysis	84 322	45 818 (54.3)	38 504 (45.7)
Cluster characteristics			
No. of practices	246	122	124
Urbanization			
High	87	48 (55.2)	39 (44.8)[b]
Low	159	74 (46.5)	85 (53.5)

[a] $P<.001$ (χ^2 test).
[b] $P=.20$ (χ^2 test).

for cytology; CIN grade 2 or 3 and their glandular equivalents for histology and high-grade SIL or adenocarcinoma in situ for cytology; and malignant (comprising squamous cell carcinoma and endocervical adenocarcinoma).

In case of varying outcomes within the same class, the reviewed histological diagnosis was used as outcome. In case the review diagnosis fell in a class other than the original diagnosis, a second experienced pathologist (or cytotechnologist in case of cytology) did a blinded review. When this second review diagnosis fell in the same class as the original or first review diagnosis, this second review diagnosis was used as the outcome. However, if the second review did not concur with the 2 previous assessments, the case was discussed using a double-headed microscope by the 2 reviewers and a consensus diagnosis was reached. This consensus diagnosis was used as the final outcome, which was categorized as CIN grade 1+ or low-grade SIL+ (including CIN grades 1, 2, and 3, carcinoma or the cytological equivalents) or CIN grade 2+ or high-grade SIL+ (including CIN grade 2 or 3, carcinoma, or the cytological equivalents).

Only participants from randomized practices were included in the intention-to-treat analysis. The per-protocol analysis included only participants who received the test determined by randomization. χ^2 Tests were used for comparison of proportions. Crude rate ratios (RRs) were computed as ratios of the DRs or the PPVs. Odds ratios (ORs) for finding a verified outcome in liquid-based cytology vs conventional Pap test, adjusted for confounding factors, were computed by logistic regression. The following confounding factors were included in multivariate analyses: age, urbanization level, study site, and period. Period was defined as the first and second half of the study, using the median preparation date as a separator. Odds ratios were converted into RRs using established methods.[14-16]

The ratios of the DR of verified cervical abnormalities in the liquid-based cytology relative to the conventional Pap test group was assessed for the primary histological outcome of CIN grades 1+, 2+, and 3+ and carcinoma. The cluster design was taken into account for calculation of 95% confidence intervals (CIs). Statistical testing was 2-sided, and significance was defined at $P<.05$. Binomial exact 95% CIs were computed around proportions. Analyses were performed using Stata 10.0 statistical software (StataCorp LP, College Station, Texas).

RESULTS

A total of 89 960 women, recruited from 327 family practices, were enrolled in the trial (FIGURE). Family practices that were not connected to 1 of the study sites but nevertheless requested cytological assessment on an occasional basis had not been randomized and were excluded from analysis (176 cases from 81 practices), leaving 89 784 participants from 246 family practices for evaluation (49 222 from 122 practices using liquid-based cytology; 40 562 from 124 practices using conventional Pap test). In the intention-to-treat analysis, another 625 inadequate smears were excluded as were the 171 cases lost to follow-up. This left 88 988 individuals for evaluation (48 941 in the liquid-based cytology group; 40 047 in the Pap test group). Moreover, in the per-protocol analysis 4666 participants who received a test other than the one to which their family practice was assigned (contaminants) were excluded resulting in 84 322 participants from 246 practices (45 818 with liquid-based cytology and 38 504 with Pap test).

Despite a balanced distribution of family practices, differences were found in the number of participants over the 2 groups (TABLE 1). By chance, 6 large practices (with 1000 women or more) belonging to the Eindhoven site and op-

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erating in urban areas were allocated to the liquid-based cytology group, whereas only 1 was allocated to the conventional Pap test group. Eindhoven is a high-volume laboratory and had evaluated considerably more slides than did the Nijmegen site. Liquid-based cytology was performed more often in high-urban areas than low ones (56.1%, high urban vs 54.2% low urban areas). A higher proportion of younger participants was examined with liquid-based cytology than were older participants ($P < .001$).

In the intention-to-treat analysis, 2474 women with cytological abnormalities were identified (TABLE 2). The follow-up results of women with abnormal cytology are given in the eFigure (available at http://www.jama.com). Most cases (56.4%) were followed up cytologically. Histology was performed in 36.3% of the cases. Six cases had only colposcopy during follow-up, and 171 cases (6.9%) were lost to follow-up. None of the differences in follow-up procedures between tests were statistically significant. Seventy-one percent of cytological borderline and low-grade abnormalities was based on revised cytological follow-up, whereas 91.2% of high-grade cytological lesions were generally verified with histology. Only 3.8% of the initial high-grade SIL+ lesions were lost to follow-up compared with 7.8% of borderline and low-grade cytology. All follow-up histology and cytology was reviewed and the result of the review was used as study outcome. Cases that were lost to follow-up were excluded from analysis.

TABLE 3 presents the intention-to-treat and per-protocol results of the DRs

Table 2. Follow-up and Verification of Test-Positive Cases

	Test Positives, No. (%) of Woman			
	Liquid-Based Cytology (n = 49 222)	Conventional Papanicolaou Test (n = 40 562)	*P* Value Difference	Total % (n = 89 784)
ASCUS/AGUS and low-grade SIL				
Cytology	725 (71.1)	642 (71.4)		71.3
Colposcopy	4 (0.4)	2 (0.2)		0.3
Histology	203 (19.9)	188 (20.9)	.343	20.4
Lost to follow-up	83 (8.1)	67 (7.5)		7.8
missing	4 (0.4)	0 (0.0)		0.2
Subtotal	1019 (100.0)	899 (100.0)	1918	100.0
High-grade SIL				
Cytology	11 (3.6)	17 (6.7)		5.0
Colposcopy	0 (0.0)	0 (0.0)	.145	0.0
Histology	277 (91.7)	230 (90.6)		91.2
Lost to follow-up	14 (4.6)	7 (2.8)		3.8
Subtotal	302 (100.0)	254 (100.0)	556	100.0
Overall				
Cytology	736 (55.7)	659 (57.2)		56.4
Colposcopy	4 (0.3)	2 (0.2)		0.2
Histology	480 (36.3)	418 (36.3)	.297	36.3
Lost to follow-up	97 (7.3)	74 (6.4)		6.9
missing	4 (0.3)	0 (0.0)		0.2
Total	1321 (100.0)	1153 (100.0)	2474	100.0

Abbreviations: ASCUS/AGUS, atypical squamous cells of undetermined significance or atypical glandular cells of undetermined significance; CIN, cervical intraepithelial neoplasia; SIL, squamous intraepithelial lesion.

Table 3. Detection Rates of Verified Histologically Confirmed Neoplasia or Cervical Cancer

Verified Histological Outcome	Liquid-Based Cytology		Conventional Papanicolaou Test		DR Ratio (95% Confidence Interval)	
	No. of Women (n = 48 941)	DR (95% CI)	No. of Women (40 047)	DR (95% CI)	Crude	Adjusted[a]
Intention-to-Treat Analysis						
CIN grade						
1+	405	0.83 (0.75-0.91)	328	0.82 (0.74-0.91)	1.01 (0.88-1.17)	1.01 (0.85-1.19)
2+	346	0.71 (0.63-0.78)	280	0.70 (0.62-0.78)	1.01 (0.86-1.18)	1.00 (0.84-1.20)
3+	253	0.52 (0.45-0.58)	190	0.47 (0.41-0.54)	1.09 (0.90-1.31)	1.05 (0.86-1.29)
Carcinoma	30	0.06 (0.04-0.08)	14	0.03 (0.02-0.05)	1.75 (0.91-3.31)	1.69 (0.96-2.99)
Per-Protocol Analysis						
	No. of Women (n = 45 818)	DR (95% CI)	No. of Women (n = 38 504)	DR (95% CI)		
CIN grade						
1+	382	0.83 (0.75-0.92)	312	0.81 (0.72-0.90)	1.03 (0.89-1.19)	1.02 (0.85-1.21)
2+	327	0.71 (0.64-0.80)	270	0.70 (0.62-0.79)	1.02 (0.87-1.20)	1.00 (0.83-1.20)
3+	235	0.51 (0.45-0.58)	181	0.47 (0.40-0.54)	1.09 (0.90-1.33)	1.04 (0.85-1.28)
Carcinoma	27	0.06 (0.04-0.09)	13	0.03 (0.02-0.06)	1.75 (0.90-3.38)	1.66 (0.90-3.03)

Abbreviation: CIN, cervical intraepithelial neoplasia; DR, detection rate.
[a] Adjusted for age, study site, urbanization level, and study period and taking the cluster design into account.

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of histologically verified CIN or carcinoma in each study group, as well as the crude and adjusted DR ratios. Irrespective of the grade of the initial cytological abnormality that triggered further follow-up, DR ratios were close to one and none significantly differed from unity.

TABLE 4 provides the correlation between the baseline cytological result and the verified outcome (histology, colposcopy, or cytology) for liquid-based cytology and conventional Pap test in the intention-to-treat analysis. With liquid-based cytology, ASCUS/AGUS resulted in 2.7% in the detection of CIN grade 3+ or severe dysplasia or cancer, 4.2% in detection of CIN grade 2 or moderate dysplasia, 5.1% in CIN grade 1 or low-grade SIL; and 88.1% in the absence of CIN or SIL. For conventional Pap tests these figures were 3.5% for CIN grade 3+, severe dysplasia, or cancer; 2.6% for CIN grade 2 or moderate dysplasia; 6.5% for CIN grade 1 or low-grade SIL; and 87.4% in absence of CIN or SIL. A liquid-based cytology result of low-grade SIL resulted in an 18.7% outcome of CIN grade 3+, severe dysplasia, or cancer; 9.1% in CIN grade 2 or moderate dysplasia; 17.1% in CIN grade 1 or low-grade SIL; and 55.1% no CIN or a verified outcome less than low-grade SIL was found. For conventional Pap test, these figures were 13.8%, 14.3%, 15.8%, and 55.9%, respectively. High-grade SIL+ in liquid-based cytology resulted in 87.1% (n=251) in verified high-grade cervical lesions compared with 81.0% (n=200) with Pap test.

The PPVs of liquid-based cytology and conventional Pap test and their ratios for different levels of test positivity and outcome thresholds are presented in TABLE 5 for both the intention-to-treat and per-protocol approaches. The PPVs of liquid-based cytology and Pap test were comparable since both the crude and adjusted PPV ratios never differed significantly from unity, irrespective of the cytological or verified outcome cut-off value.

COMMENT

The performance of liquid-based cytology and conventional Pap test were prospectively compared in terms of DRs and PPVs for cervical cancer precursors. This was done in a large-scale, population-based, cluster randomized controlled trial including almost 90 000 participants. To our knowledge, this is the largest high-quality study performed in a population-based setting with blind verification of follow-up outcomes of all test-positive cases contrasting with many previous studies, which often suffer from methodological flaws.[4,5] Despite careful cluster randomization, the distribution of individuals between the 2 study groups was unbalanced. This was the result of allocation of a few large family practice centers to the experimental group. These centers were mainly serving densely populated areas. However, we controlled for possible confounding by applying multivariable logistic regression with correction for cluster effects.

As shown in a previous publication, no differences were found in the cytological test positivity rates between methods.[8] Nevertheless, these cytological findings contribute insufficient evi-

Table 4. Baseline Cytology vs Verified Follow-up Outcome

Baseline Cytology	No. of Women	Verified Follow-up Outcome, No. (%) [95% Confidence Interval]: Within Normal Limits, ATYPIA, or ASCUS	CIN Grade 1 or Low-Grade SIL	CIN Grade 2 or Moderate Dysplasia	CIN Grade 3+ or Severe Dysplasia	*P* Value[a]
Intention-to-Treat Analysis						
ASCUS/AGUS						
Liquid-based cytology	725	656 (88.1) [85.5-90.3]	38 (5.1) [3.6-6.9]	31 (4.2) [2.8-5.9]	20 (2.7) [1.6-4.1]	.22
Conventional Pap test	680	594 (87.4) [84.6-89.8]	44 (6.5) [4.7-8.6]	18 (2.6) [1.6-4.2]	24 (3.5) [2.3-5.2]	
Low-grade SIL						
Liquid-based cytology	187	103 (55.1) [47.7-62.3]	32 (17.1) [12.0-23.3]	17 (9.1) [5.4-14.2]	35 (18.7) [13.4-25.8]	.33
Conventional Pap test	152	85 (55.9) [47.6-64.0]	24 (15.8) [10.4-22.6]	22 (14.3) [9.3-21.1]	21 (13.8) [8.8-20.0]	
High grade SIL+						
Liquid-based cytology	288	21 (7.3) [4.6-10.9]	16 (5.6) [3.2-8.9]	52 (18.1) [13.8-23.0]	199 (69.1) [63.4-74.4]	.08
Conventional Pap test	247	31 (12.6) [8.7-17.3]	16 (6.5) [3.7-10.3]	53 (21.5) [16.5-27.1]	147 (59.5) [53.1-65.7]	
Per-Protocol Analysis						
ASCUS/AGUS						
Liquid-based cytology	696	613 (88.1) [84.4-90.4]	35 (5.0) [3.5-6.9]	28 (4.0) [2.7-5.8]	20 (2.9) [1.8-4.4]	.53
Pap test	640	563 (88.0) [82.2-90.4]	38 (5.9) [4.2-8.1]	18 (2.8) [1.7-4.4]	21 (3.3) [2.0-5.0]	
Low-grade SIL						
Liquid-based cytology	179	98 (54.8) [47.2-62.2]	31 (17.3) [12.1-23.7]	16 (8.9) [5.2-14.1]	34 (19.0) [13.5-23.5]	.42
Conventional Pap test	149	85 (57.1) [48.7-65.1]	23 (15.4) [10.0-22.3]	21 (14.1) [8.9-20.7]	20 (13.4) [8.4-20.0]	
High-grade SIL						
Liquid-based cytology	269	21 (7.8) [5.0-11.9]	15 (5.6) [3.2-9.2]	51 (19.0) [14.8-24.7]	182 (67.7) [63.2-74.7]	.23
Conventional Pap test	238	30 (12.6) [8.7-17.5]	14 (5.9) [3.2-9.7]	52 (21.9) [16.8-27.6]	142 (59.7) [53.1-66.0]	

Abbreviations: ATYPIA or ASCUS, atypical epithelium or atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia grade; Pap, Papanicolaou; SIL, squamous epithelial lesion.
[a] χ^2 test.

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dence to claim equal diagnostic accuracy. Both the intention-to-treat and per-protocol analyses demonstrated that liquid-based cytology was not superior to Pap test regarding detection rates of histologically confirmed outcomes. The same was found for the PPVs. Altogether, these findings provide strong evidence that the performance of liquid-based cytology is not superior to that of the conventional Pap test when applied within a well-organized and quality-controlled cervical screening program.

These findings partly contrast the results of other studies comparing performance of the 2 methods.[17-39] Most studies used a nonrandomized study design and compared only cytological test positivity rates. Only a limited number focused on biopsy-confirmed cervical lesions or (blind) gold standard verification.

The results of systematic reviews varied depending on the quality criteria for inclusion of individual studies.[4-7] Our results are in line with those of a recently published meta-analysis, including only clinical studies with complete gold standard verification or randomized screening trials with nearly complete verification of cytological abnormalities.[5]

A randomized study design was applied in only 3 other studies.[40-42] One study was underpowered (n=1999) but also found no difference in the performance of the 2 methods.[40] Another, large-scale study (n=45 174) by Ronco et al[41] found no statistically significant difference for detection of CIN grade 2+ between liquid-based cytology and conventional Pap test but reported a reduced PPV for liquid-based cytology. This was in contrast with the current trial, the result of an increased frequency of minor cytological abnormalities with liquid-based cytology without an increase in high-grade CIN on histology. Similar to our study, they reported a significant decrease in unsatisfactory rates too. Finally, in a smaller study (n=13 484) by Strander et al,[42] liquid-based cytology detected significantly more high-grade lesions, but this was at the expense of a 30% increase in abnormal cytology samples.[43]

In contrast, our study found no difference in sensitivity in terms of histological detection rates of cervical lesions or in the PPV between liquid-based cytology and Pap test, indicating that the accuracy of both methods is comparable.[44] This may be caused by high-quality standards of conventional screening in the Netherlands.

Because of randomization, it can plausibly be assumed that the prevalence of CIN was equal in both study groups. Therefore, the lack of difference in DR and PPV in this trial demonstrates that liquid-based cytology is neither more sensitive nor more specific in detecting cervical cancer precursors than the conventional Pap smear. A reduced unsatisfactory rate was found when using liquid-based cytology,[8] even though the added value was limited because the unsatisfactory rates were already low. On the other hand, liquid-based cytology tests cost more money than a conventional Pap test, but in equivocal cases it has the possibility of concomitant testing on the residual material for the presence of hrHPV

Table 5. Positive Predictive Values of Liquid-Based Cytology vs Conventional Papanicolaou Test

	Liquid-Based Cytology		Conventional Papanicolaou Test		PPV Ratio (95% CI)	
	No. of Cases	PPV (95% CI)	No. of Cases	PPV (95% CI)	Crude	Adjusted[a]
Intention-to-Treat Analysis						
Baseline cytology ASCUS	1220		1079			
CIN grade 1+ or low-grade SIL+	440	36.1 (33.4-38.8)	369	34.2 (31.4-37.0)	1.05 (0.94-1.18)	0.97 (0.81-1.18)
CIN grade 2+ or high-grade SIL+	354	29.1 (26.5-31.6)	285	26.4 (23.8-29.0)	1.10 (0.96-1.25)	0.99 (0.80-1.22)
Baseline cytology low-grade SIL+	475		399			
CIN grade 1+ or low-grade SIL+	351	73.9 (69.9-77.9)	283	70.0 (66.5-75.4)	1.04 (0.95-1.13)	1.03 (0.74-1.42)
CIN grade 2+ or high-grade SIL+	303	63.8 (59.5-68.1)	243	60.9 (56.1-65.7)	1.05 (0.94-1.16)	1.03 (0.66-1.78)
Baseline cytology high-grade SIL+	288		247			
CIN grade 2+ or high-grade SIL+	251	87.1 (83.3-91.0)	200	81.0 (76.0-85.9)	1.08 (0.99-1.16)	1.08 (0.67-1.75)
Per-Protocol Analysis						
Baseline cytology ASCUS+	1114		1027			
CIN grade 1+ or low-grade SIL+	412	36.0 (33.2-38.9)	349	34.0 (31.1-37.0)	1.06 (0.94-1.19)	0.99 (0.81-1.21)
CIN grade 2+ or high-grade SIL+	331	28.9 (26.3-31.7)	274	26.7 (24.0-29.5)	1.08 (0.94-1.24)	0.99 (0.79-1.23)
Baseline cytology low-grade SIL+	448		387			
CIN grade 1+ or low-grade SIL+	329	73.4 (69.1-77.5)	272	70.3 (65.5-74.8)	1.04 (0.96-1.14)	1.06 (0.76-1.49)
CIN grade 2+ or high-grade SIL+	283	63.2 (58.5-67.6)	235	60.7 (55.7-65.6)	1.04 (0.93-1.16)	1.04 (0.77-1.40)
Baseline cytology high-grade SIL+	269		238			
CIN grade 2+ or high-grade SIL+	233	86.6 (82.0-90.4)	194	81.5 (76.0-86.2)	1.06 (0.98-1.15)	1.09 (0.66-1.79)

Abbreviations: ASCUS, atypical squamous cells of undetermined significance; CI, confidence interval; CIN, cervical intraepithelial neoplasia grade; PPV, positive predictive value; SIL, squamous epithelial lesion.
[a] Adjusted for age, study site, urbanization level and study period, taking clustering into account.

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or other molecular cell cycle–related biomarkers.

In conclusion, liquid-based cytology is neither more sensitive nor more specific in detecting CIN or cancer.

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