Relation between sampling device and detection of abnormality in cervical smears: a meta-analysis of randomised and quasi-randomised studies

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Abstract

Objective—To assess the diagnostic yield of different sampling devices used in cervical screening.

Design—Meta-analysis of randomised and quasi-randomised studies.

Setting—All randomised and quasi-randomised studies comparing the yield of cytological or histological abnormalities when two or more different sampling devices were used.

Subjects—85 000 patients included in 29 studies reported in 28 papers.

Main outcome measures—Pooled relative risk and 95% confidence interval of the yield of mild dysplasia or worse in smears recovered by each sampling method versus each other method with which it was compared; sensitivity or positive predictive value, or both, of cytological versus histological results in six studies from which sufficient data were available.

Results—There were no substantial differences in the yield of cytological abnormalities between the Ayre spatula, the Cytobrush, and the cotton swab used alone. There were also no substantial differences in the yield of cytological abnormalities between the extended tip spatula, the Ayre spatula combined with the Cytobrush or cotton swab, or the Cervex brush. The Ayre spatula, Cytobrush, or cotton swab used alone generally performed significantly worse than the combinations, the extended tip spatula, or the Cervex brush. There were no substantial differences in sensitivity or positive predictive value between the sampling methods.

Conclusions—These results support the use of either the extended tip spatula, a combination of any spatula plus the Cytobrush or cotton swab, or the Cervex brush for cervical screening.

Introduction

During 50 years after the first publications on cervical screening^{1,2} and 30 years after the initial method of vaginal aspiration was abandoned³ several studies assessed the relative value of newer sampling methods. However, because of lack of statistical significance resulting from variations in the designs of the studies and small numbers in many we still do not know which sampling device is best.

In a previous review Buntinx *et al* found that using a spatula and the Cytobrush in combination yielded the highest proportion of smears with endocervical or metaplastic cells,⁴ an important indicator of sampling quality. The question remains, however, whether improved cervical sampling will lead to higher diagnostic yield. In order to determine which method achieves the best diagnostic yield we reviewed published randomised and quasi-randomised studies comparing

the effects of different sampling techniques on the proportion of pathological smears recovered.

In most studies cytological criteria (proportions of smears showing dysplasia) are used as a measure of outcome. Some studies also present histological data. These results permit the additional calculation of sensitivity or positive predictive value, or both, for each sampling method.

Methods

RETRIEVAL OF PAPERS

An on line Medline search was augmented by a similar check of FAMILI (Family Literature Index), by carefully screening the references in all articles, and by contacting experts in the subject. "Cervix—neoplasms/Prevention and control" and "Vaginal—smears/all sub-headings" were used as keywords for the initial computer search. Searches were updated to the end of 1994. No language restrictions were used. Publication bias was examined by using funnel plots for those comparisons for which at least four studies were available.

SELECTION OF PAPERS

Initially all controlled studies examining the relation between the presence of abnormality in a smear and the type of sampling device were selected. Generally in this review when cytological results are used as the outcome measure they refer to mild dysplasia or worse. When histological results are used they refer to a diagnosis of at least grade I cervical intraepithelial neoplasia or at least grade III cervical intraepithelial neoplasia in tissues obtained by biopsy or cone biopsy or during surgery. Papers were excluded if they lacked the necessary data; if no randomised, quasi-randomised, or paired design was used; or if methods or outcome were insufficiently defined.

Extended tip spatulas—that is, spatulas whose tips have been extended to permit endocervical sampling—exist in multiple shapes and materials. Though this may influence the recovery of pathological smears, all spatulas were classified as either classic Ayre spatulas or extended tip spatulas. When details were missing spatulas were assigned to the extended tip group.

Some studies lasted several years. As the numbers of smears examined increased so the credibility and precision of the studies increased. Some accounts were of studies to be followed up years later by a second report that covered a longer period.⁵⁻⁹ In these cases the most recent report was used. One report describing two completely different studies was treated as two separate reports.¹⁰

METHODOLOGICAL STRENGTH

Study methodology was reviewed by systematically identifying the number of smears examined, the setting of the study (population based, unselected, referred, or otherwise selected patients), the type of assignment of

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each patient to a sampling method (paired with or without randomisation of the sequence, randomisation, or quasi-randomisation), and the outcome measures (cytological or histological, or both). These indicators were judged independently by two reviewers, rare discordances being decided by consensus.

DESCRIPTIVE ANALYSIS

The relative risk and 95% confidence interval of the proportion of cytological abnormalities in smears obtained with one device versus another were used to express the results of the various studies.^{11 12} When histological data were available we used these as the standard when calculating sensitivity and positive predictive value (and 95% confidence intervals) of the cytological result. These were estimated separately for mild dysplasia or worse and severe dysplasia or worse (cytological) versus at least grade I cervical intraepithelial neoplasia and at least grade III cervical intraepithelial neoplasia (histological).

For all comparisons we estimated the statistical power of all available studies to detect a relative risk of 1.25. Therefore, standard errors were calculated from the confidence intervals after logistic transformation. Results below 0.99 were rounded to the nearest 5%.

STATISTICAL POOLING

Pooled relative risks and their 95% confidence intervals were calculated by a Mantel-Haenszel estimation. However, when the χ^2 test showed significant heterogeneity between studies a random effects method was applied by means of Fast-Pro 1.7 software.¹³

Results

Of 41 papers retrieved, 13 were excluded because of lacking essential crude data,^{14 15} the use of a cohort^{16 17} or pre-post^{2 6 15 18-21} design, extreme selection of patients,²² inadequate definition of method²³ or outcome,²⁴ or reporting partial results from a study on which a later report was available.⁵ One report described two different studies, which we considered separately.¹⁰ The 28 papers selected for the review therefore covered 29 studies.^{10 25-51} Seven studies concerned screening a non-selected population. In all other studies patients were selected or referred, generally for further evaluation after an abnormal smear. Ten studies used a paired design, two or more methods being used for the same patients during the same examination. In 18 studies patients were assigned to a method by randomisation ($n = 8$) or quasi-randomisation ($n = 10$) (table 1). All studies presented cytological data for analysis, and in eight studies histological data were available also (table 1).

CYTOLOGICAL RESULTS

χ^2 Tests indicated significant between study heterogeneity in cytological findings in one comparison only. When comparing an extended tip spatula and the Cytobrush (with mild dysplasia used as cut off) heterogeneity seemed to be associated with one study¹⁰ showing a very high relative risk (7.32) based on 17 pathological smears only. Removing this study resulted in homogeneity with a significant relative risk of 0.93 (table 2). Only for the comparison of spatula plus Cytobrush versus spatula plus cotton swab did the funnel plot suggest publication bias in favour of the spatula plus Cytobrush. (A copy of all funnel plots is available from FB.)

Mild dysplasia or worse as outcome measure

Ayre spatula—A combination of the Ayre spatula plus an endocervical device (cotton swab or Cytobrush) performed better than the Ayre spatula used alone in detecting dysplasia. Pooling of paired studies only resulted in a pooled relative risk of 1.13 (95%

confidence interval 1.03 to 1.24) for the combination including the Cytobrush. Both studies comparing the Ayre spatula with the Ayre spatula plus cotton swab used a paired design. The extended tip spatula and the Cervex brush also performed better than the Ayre spatula, though not significantly so. Studies were in referred patients as well as in unselected populations. Results of all comparisons were homogeneous.

Extended tip spatulas performed better than the Ayre spatula or the endocervical devices used alone. Results with extended tip spatulas were comparable to those with the Ayre spatula plus Cytobrush combination (relative risk 1.02), the Cervex brush (1.00), and the Cytopick (0.92).

Cytobrush or cotton swab alone—Using the Cytobrush alone resulted in a higher yield of cytological abnormalities than with the cotton swab used alone (relative risk 1.41). Both devices, however, performed significantly worse than most devices with which they were compared. Comparisons with the Ayre spatula and extended tip spatulas gave non-significant results.

Ayre spatula plus cotton swab or Cytobrush—The combination of Ayre spatula plus cotton swab or Cytobrush performed significantly better than the Ayre spatula, cotton swab, or (for spatula plus cotton swab only) Cytobrush used alone. Comparisons of these combinations showed no significant differences. However, power for these comparisons was below 0.50.

Extended tip spatula plus cotton swab or Cytobrush—Comparison of the combination of extended tip spatula plus cotton swab or Cytobrush with extended tip spatula, Cervex brush, or Cytopick used alone generally showed no significant differences. Power was low for most studies of spatula plus the Cytobrush. The one (low power) study comparing the combinations showed a better, though non-significant outcome for the extended tip spatula plus the Cytobrush. When using either the Ayre spatula plus cotton swab or the Ayre spatula alone (depending of an everted Cervex ($n = 252$)), Garite and Feldman detected mild dysplasia or worse in 5% of smears, which was comparable to the 4.5% when using the spatula alone and much less than when using the combination (11%).³⁰

Cervex brush—In none of the six comparisons including the Cervex brush was a significantly better or worse outcome recorded. Four of the six comparisons had high statistical power.

Other devices—No significant difference was found in any comparison including the Cytopick, a combination of Ayre spatula plus aspirator, the Profile brush, or the Bayne brush. In one paired study significantly more smears containing mild dysplasia or worse were obtained with the Multispatula than with the Ayre spatula.³⁷ No comparison was examined in more than one study. Most studies had small sample sizes.

Severe dysplasia or worse as outcome measure

The results of most studies using severe dysplasia or worse as the outcome measure followed the trends of the those using mild dysplasia or worse as the outcome measure. Generally sample sizes were small and the results non-significant. The Ayre spatula plus cotton swab combination and the extended tip spatula plus cotton swab or Cytobrush combination, however, performed significantly better than the Ayre spatula and extended tip spatula, respectively.

HISTOLOGICAL COMPARISONS

Sensitivities and positive predictive values of smears obtained with different devices were similar. Almost all values were well within the 95% confidence intervals of the other values. Sample sizes for all these analyses were generally small, with denominators between 31 and 348.

Table 1—Methodological details of the 29 selected studies

First author, year of publication, and country	Setting	Method of assignment	Devices†	No of smears	Outcome	Remarks‡
Boon 1989, Netherlands ²⁷	Screening, population based	Quasi-random (weekly alternation)	Ext tip Ext tip + Cytob Cytobick Ext tip + cott Cervex	9140 4142 3406 3200 2627	Cytology	"Modified Ayre" spatula
Bounds 1976, United Kingdom ⁵⁰	Screening, family planning/postnatal	Random	Ayre Ext tip	491 491	Cytology	Armovical spatula
Buntinx 1991, Netherlands ²⁸	Collection of mainly pathological smears	Paired (fixed sequence)	Ext tip Cytob Ext tip + Cytob	444 444 444	Cytology	
Fokke 1993, Netherlands ²⁹	Gynaecological clinic	Random	Ayre Ayre + Cytob Cervex	87 92 90	Cytology	
Garite 1978, United States ³⁰	Gynaecological clinic	Quasi-random (monthly alternation)	Ext tip Ext tip + cott	222 173	Cytology	No details about type of spatula available
Glenthøj 1988, Germany ³¹	Referred for cone biopsy	Random	Cytob Cott	50 50	Cytology/histology	Biopsy proved CIN III or more
Gormey 1989, United Kingdom ³²	Genitourinary department	Quasi-random (4 monthly alternation)	Ayre Ext tip	2077 2003	Cytology	Aylesbury
Hoffman 1991, United States ³³	Referred for abnormal smear	Paired (fixed sequence)	Ayre + cott Cytob	348 348	Cytology/histology	All patients had biopsy proved cervical neoplasia or human papillomavirus
Hutchinson 1991, United States ³⁴	Both screening and referred patients	Quasi-random (alternation)	Ext tip + Cytob Cervex	213 253	Cytology	"Modified Ayre" spatula
Johansen 1979, Denmark ²⁵	Referred for abnormal smear	Paired (fixed sequence)	Ayre Cott Ayre + cott	182 182 182	Cytology/histology	Satisfactory smears only
Koonings 1992, United States ³⁵	Referred for abnormal smear	Random	Ext tip + Cytob Ext tip + cott	147 143	Cytology/histology	Milex
Longfield 1993, United Kingdom ³⁶	Screening as well as follow up	Random	Profile Ayre + Cytob	491 489	Cytology	Recent diathermy in 184 patients
Metcalfe 1994, United Kingdom ⁵¹	Referred patients	Random	Ayre Ext tip Multispatula Ayre + Cytobrush	330 331 199 203	Cytology/histology	After 824 smears sampling was restricted to Ayre/ext tip (Aylesbury) device. All patients had histologically proved CIN ≥ II
Pistofides 1988, United Kingdom ³⁷	Referred for abnormal smear	Paired (random sequence)	Ayre Multispatula	158 158	Cytology	
Pretorius 1991, United States ³⁸	Screening	Random	Bayne Ayre + Cytob Ayre + cott	4320 3422 3319	Cytology/histology§	Not pregnant
Rammou-Kinia 1991, Greece ³⁹	Screening	Paired (fixed sequence)	Cott Ayre Cytob Ext tip	109 109 109 109	Cytology	Non-pregnant, premenopausal, Szalay (Ext tip)
Rivlin 1993, United States ⁴⁰	Initial prenatal visit	Paired (sequence changed once)	Ayre + Cytob Ayre + cott	222 222	Cytology	All pregnant
Schettino 1993, Italy ⁴¹	Referred for abnormal smear	Paired (fixed sequence)	Ayre Cytob Cott Ayre + Cytob Ayre + cott	89 89 89 89 89	Cytology	
Selvaggi 1991, United States ⁴²	Mostly referred for abnormal smear	Random	Ext tip + Cytob Ext tip + bulb aspirator	90 102	Cytology/histology§	"Modified Ayre" spatula
Szarewski 1990, United Kingdom ⁴³	Department of genitourinary medicine	Quasi-random (monthly alternation)	Ayre Ext tip Ayre + Cytob Cervex	1784 1637 1769 1801	Cytology	Aylesbury, 89% aged less than 35
Szarewski 1991, United Kingdom ⁴⁹	Follow up after laser treatment	Quasi-random (monthly alternation)	Cervex Ayre + Cytobrush	421 381	Cytology	
Szarewski 1993, United Kingdom ⁴⁴	Family planning clinic	Quasi-random (monthly alternation)	Ext tip 1 Cervex Ext tip 2 Ext tip 1 + Cytob	3614 3828 3389 3341	Cytology	Ext tip: 1 = Aylesbury, 2 = Rolon
Van Erp 1988, Netherlands ⁴⁵	Referred for abnormal smear	Paired (fixed sequence)	Ayre Ayre + Cytob	130 130	Cytology	
Van Erp 1989, Netherlands ⁴⁶	Screening	Paired (fixed sequence)	Ayre Ayre + Cytob	632 632	Cytology	Family planning clinic
Vooijs 1988, Netherlands ^{10a}	Screening	Quasi-random (alternation)	Ext tip Cytob	852 832	Cytology	Population screening programme. Satisfactory smears only
Vooijs 1988, Netherlands ^{10b}	Screening	Quasi-random (alternation)	Ext tip Cervex	710 754	Cytology	Population screening programme. Satisfactory smears only
Waddel 1990, United Kingdom ²⁶	Referred patients	Paired (random sequence)	Ayre Cervex	280 280	Cytology/histology	Histology on indication only
Wolfendale 1987, United Kingdom ⁴⁷	Smears taken outside hospital	Crossover	Ayre Ext tip	7862 7971	Cytology	
Woodman 1991, United Kingdom ⁴⁸	Referred patients	Quasi-random (weekly alternation)	Ayre Ext tip	248 285	Cytology	Rocket

†Ext tip = Extended tip spatula. Cytob = Cytobrush. Cott = Cotton swab.

‡CIN = Cervical intraepithelial neoplasia.

§Estimation of sensitivity on positive predictive value impossible owing to insufficient data.

Table 2—Diagnostic yield in each study with power, χ^2 test for heterogeneity, pooled relative risk, and 95% confidence interval for each comparison

Method 1	Method 2	Cut off	Reference No	Pathology†				Relative risk (95% confidence interval)	Pooled relative risk (95% confidence interval)	Power	P value for homogeneity
				(+) I	(-) I	(+) II	(-) II				
Ayre + cotton swab	Ayre	Mild	25	127	55	101	81	1.26 (1.07 to 1.48)	1.29 (1.12 to 1.49)	0.85	0.55
		41	54	35	39	50	1.38 (1.04 to 1.85)				
Ayre + cotton swab	Cotton swab	Severe	25	61	121	53	129	1.15 (0.85 to 1.56)	1.15 (0.85 to 1.56)	<0.50	—
		Mild	25	127	55	112	70	1.13 (0.98 to 1.32)			
Ayre + cotton swab	Cytobrush	Severe	41	54	35	39	50	1.38 (1.04 to 1.85)	1.20 (1.05 to 1.37)	0.95	0.21
		Mild	25	61	121	40	142	1.52 (1.08 to 2.15)			
Ayre + Cytobrush	Ayre	Severe	33	256	92	191	157	1.34 (1.20 to 1.50)	1.52 (1.08 to 2.15)	<0.50	—
		Mild	41	54	35	47	42	1.15 (0.89 to 1.49)			
Ayre + Cytobrush	Ayre	Severe	51	51	152	79	251	1.05 (0.77 to 1.42)	1.08 (0.97 to 1.21)	0.95	0.30
		Mild	29	5	87	8	79	0.59 (0.20 to 1.74)			
Ayre + Cytobrush	Cervex	Severe	41	57	32	39	50	1.46 (1.10 to 1.94)	1.06 (0.94 to 1.20)	0.85	0.33
		Mild	43	400	1369	380	1404	1.06 (0.94 to 1.20)			
Ayre + Cytobrush	Cervex	Severe	46	73	559	63	569	1.16 (0.84 to 1.59)	1.00 (0.89 to 1.12)	0.85	0.33
		Mild	29	5	87	8	82	0.61 (0.21 to 1.80)			
Ayre + Cytobrush	Ayre + cotton swab	Severe	43	400	1369	401	1400	1.02 (0.90 to 1.15)	2.74 (0.54 to 13.87)	<0.50	—
		Mild	49	23	358	30	391	0.85 (0.50 to 1.43)			
Ayre + Cytobrush	Cervix	Severe	49	5	376	2	419	2.74 (0.54 to 13.87)	2.74 (0.54 to 13.87)	<0.50	—
		Mild	38	51	3371	45	3274	1.10 (0.74 to 1.64)			
Ayre + Cytobrush	Cervix	Severe	40	18	204	18	204	1.00 (0.53 to 1.87)	1.09 (0.81 to 1.48)	<0.50	0.97
		Mild	41	57	32	54	35	1.06 (0.84 to 1.33)			
Ayre + Cytobrush	Cervix	Severe	41	57	32	47	42	1.21 (0.94 to 1.56)	1.21 (0.94 to 1.56)	<0.50	—
		Mild	41	57	32	39	50	1.46 (1.10 to 1.94)			
Ayre + Cytobrush	Cervix	Severe	43	400	1369	364	1273	1.02 (0.90 to 1.15)	1.00 (0.89 to 1.12)	0.99	0.43
		Mild	51	51	152	92	239	0.90 (0.67 to 1.21)			
Ayre + Cytobrush	Cervix	Severe	51	51	152	52	147	0.96 (0.69 to 1.34)	0.96 (0.69 to 1.34)	<0.50	—
		Mild	36	15	474	14	477	1.08 (0.52 to 2.20)			
Ayre + Cytobrush	Cervix	Severe	29	8	82	8	79	0.97 (0.38 to 2.46)	1.09 (0.98 to 1.21)	0.99	0.27
		Mild	43	401	1400	380	1404	1.05 (0.92 to 1.18)			
Cotton swab	Ayre	Severe	26	112	168	87	193	1.29 (1.03 to 1.61)	1.07 (0.92 to 1.25)	0.80	0.70
		Mild	25	112	70	101	81	1.11 (0.93 to 1.32)			
Cytobrush	Ayre	Severe	39	3	106	4	105	0.75 (0.17 to 3.27)	0.75 (0.53 to 1.08)	<0.50	—
		Mild	41	39	50	39	50	1.00 (0.72 to 1.39)			
Cytobrush	Cotton swab	Severe	25	40	142	53	129	0.75 (0.53 to 1.08)	1.19 (0.88 to 1.61)	<0.50	0.76
		Mild	39	4	105	4	105	1.00 (0.26 to 3.90)			
Cytobrush	Cotton swab	Severe	41	47	42	39	50	1.21 (0.89 to 1.64)	1.41 (1.14 to 1.74)	<0.56	0.23
		Mild	31	45	5	26	24	1.73 (1.31 to 2.29)			
Extended tip	Ayre	Severe	39	4	105	3	106	1.33 (0.31 to 5.82)	1.11 (1.01 to 1.21)	0.99	0.40
		Mild	41	47	42	39	50	1.21 (0.89 to 1.64)			
Extended tip	Ayre	Severe	51	92	239	79	251	1.16 (0.90 to 1.50)	1.11 (1.01 to 1.21)	0.99	0.40
		Mild	32	66	1937	70	2007	0.98 (0.70 to 1.36)			
Extended tip	Ayre	Severe	39	5	104	4	105	1.25 (0.34 to 4.53)	1.00 (0.91 to 1.09)	>0.99	0.99
		Mild	43	364	1273	380	1404	1.04 (0.92 to 1.19)			
Extended tip	Ayre	Severe	47	279	7692	228	7634	1.21 (1.02 to 1.43)	1.26 (0.99 to 1.38)	0.99	0.23
		Mild	50	15	476	7	484	2.14 (0.88 to 5.20)			
Extended tip	Cervix	Severe	32	11	1992	16	2061	0.71 (0.33 to 1.53)	1.00 (0.91 to 1.09)	>0.99	0.99
		Mild	47	88	7883	63	7799	1.38 (1.00 to 1.90)			
Extended tip	Cervix	Severe	48	129	156	101	147	1.11 (0.91 to 1.35)	1.00 (0.91 to 1.09)	>0.99	0.99
		Mild	27	52	9088	14	2613	1.07 (0.59 to 1.92)			
Extended tip	Cervix	Severe	43	364	1273	401	1400	1.00 (0.88 to 1.13)	0.93 (0.37 to 2.33)	<0.50	0.83
		Mild	44	357	3257	380	3448	1.00 (0.87 to 1.14)			
Extended tip	Cervix	Severe	10b	10	700	12	742	0.88 (0.38 to 2.04)	1.06 (0.80 to 1.42)	<0.50	—
		Mild	27	12	9128	4	2623	0.86 (0.28 to 2.67)			
Extended tip	Cervix	Severe	10b	3	707	3	751	1.06 (0.22 to 5.24)	1.06 (0.80 to 1.42)	<0.50	—
		Mild	51	92	239	52	147	1.06 (0.80 to 1.42)			
Extended tip	Cervix	Severe	39	5	104	3	106	1.67 (0.41 to 6.80)	1.67 (0.41 to 6.80)	<0.50	—
		Mild	28	369	75	400	44	0.92 (0.88 to 0.97)			
Extended tip	Cervix	Severe	39	5	104	4	105	1.25 (0.34 to 4.53)	1.71 (0.56 to 5.23)	<0.50	< 0.001
		Mild	10a	15	837	2	830	7.32 (1.68 to 31.93)			
Extended tip	Cervix	Severe	28	250	194	282	162	0.89 (0.80 to 0.99)	0.92 (0.61 to 1.40)	<0.50	0.16
		Mild	10a	3	849	1	831	2.93 (0.31 to 28.11)			
Extended tip	Cervix	Severe	27	52	9088	21	3385	0.92 (0.56 to 3.25)	0.92 (0.56 to 3.25)	<0.50	—
		Mild	27	12	9128	7	3399	0.64 (0.56 to 3.25)			
Extended tip + cotton swab	Cervix	Severe	27	18	3182	52	9088	0.99 (0.58 to 1.69)	1.35 (0.56 to 3.25)	<0.50	0.05
		Mild	30	19	154	10	212	2.44 (1.16 to 5.11)			
Extended tip + cotton swab	Cervix	Severe	27	4	3196	12	9128	0.95 (0.31 to 2.95)	0.89 (0.32 to 2.46)	<0.50	0.77
		Mild	30	1	172	2	220	0.64 (0.06 to 7.02)			
Extended tip + cotton swab	Cervix	Severe	27	18	3182	14	2613	1.06 (0.53 to 2.12)	1.06 (0.53 to 2.12)	<0.50	—
		Mild	27	4	3196	4	2623	0.82 (0.21 to 3.28)			
Extended tip + cotton swab	Cervix	Severe	27	18	3182	21	3385	0.91 (0.49 to 1.71)	0.82 (0.21 to 3.28)	<0.50	—
		Mild	27	4	3196	7	3399	0.61 (0.18 to 2.08)			
Extended tip + Cytobrush	Cervix	Severe	27	29	4113	14	2613	1.31 (0.70 to 2.48)	0.61 (0.18 to 2.08)	<0.50	—
		Mild	34	17	196	20	233	1.01 (0.54 to 1.88)			
Extended tip + Cytobrush	Cervix	Severe	44	312	3029	380	3448	0.94 (0.82 to 1.08)	0.96 (0.84 to 1.10)	0.99	0.49
		Mild	27	29	4113	52	9088	1.23 (0.78 to 1.94)			
Extended tip + Cytobrush	Cervix	Severe	28	412	32	369	75	1.12 (1.06 to 1.17)	1.05 (0.98 to 1.13)	0.99	0.19
		Mild	44	312	3029	357	3257	0.95 (0.82 to 1.09)			
Extended tip + Cytobrush	Cervix	Severe	45	44	86	35	95	1.26 (0.87 to 1.82)	1.23 (1.11 to 1.36)	0.99	0.72
		Mild	27	9	4133	12	9128	1.66 (0.70 to 3.92)			
Extended tip + Cytobrush	Cervix	Severe	28	304	140	250	194	1.22 (1.10 to 1.35)	1.00 (0.06 to 13.82)	<0.50	—
		Mild	45	1	129	1	129	1.00 (0.06 to 13.82)			
Extended tip + Cytobrush	Cervix	Severe	27	29	4113	21	3385	1.14 (0.65 to 1.99)	1.14 (0.65 to 1.99)	<0.50	—
		Mild	27	9	4133	7	3399	1.06 (0.39 to 2.84)			
Extended tip + Cytobrush	Cervix	Severe	28	412	32	400	44	1.03 (0.99 to 1.07)	1.06 (0.39 to 2.84)	<0.50	—
		Mild	28	304	140	282	162	1.08 (0.98 to 1.19)			
Extended tip + Cytobrush	Cervix	Severe	27	29	4113	18	3182	1.24 (0.69 to 2.24)	1.03 (0.99 to 1.07)	0.99	—
		Mild	35	82	65	81	62	0.98 (0.80 to 1.21)			
Extended tip + Cytobrush	Cervix	Severe	35	50	97	45	98	1.08 (0.78 to 1.50)	1.08 (0.78 to 1.50)	0.50	—
		Mild	42	11	79	17	85	0.73 (0.36 to 1.48)			
Extended tip + Cytobrush	Cervix	Severe	42	11	79	17	85	0.73 (0.36 to 1.48)	0.73 (0.36 to 1.48)	<0.50	—
		Mild	42	11	79	17	85	0.73 (0.36 to 1.48)			
Extended tip + Cytobrush	Cervix	Severe	42	11	79	17	85	0.73 (0.36 to 1.48)	0.73 (0.36 to 1.48)	<0.50	—
		Mild	42	11	79	17	85	0.73 (0.36 to 1.48)			
Extended tip + Cytobrush	Cervix	Severe	42	11	79	17	85	0.73 (0.36 to 1.48)	0.73 (0.36 to 1.48)	<0.50	—
		Mild	42	11	79	17	85	0.73 (0.36 to 1.48)			
Extended tip + Cytobrush	Cervix	Severe	42	11	79	17	85	0.73 (0.36 to 1.48)	0.73 (0.36 to 1.48)	<0.50	—
		Mild	42	11	79	17	85	0.73 (0.36 to 1.48)			
Extended tip + Cytobrush	Cervix	Severe	42	11	79	17	85	0.73 (0.36 to 1.48)	0.73 (0.36 to 1.48)	<0.50	—
		Mild	42	11	79	17	85	0.73 (0.36 to 1.48)			
Extended tip + Cytobrush	Cervix	Severe	42	11	79	17	85	0.73 (0.36 to 1.48)	0.73 (0.36 to 1.48)	<0.50	—
		Mild	42	11	79	17	85	0.73 (0.36 to 1.48)			
Extended tip + Cytobrush	Cervix	Severe	42	11	79	17	85	0.73 (0.36 to 1.48)	0.73 (0.36 to 1.48)	<0.50	—
		Mild	42	11	79	17	85	0.73 (0.36 to 1.48)			
Extended tip + Cytobrush	Cervix	Severe	42	11	79	17	85	0.73 (0.36 to 1.48)	0.73 (0.36 to 1.48)	<0.50	—
		Mild	42	11	79	17	85	0.73 (0.36 to 1.48)			
Extended tip + Cytobrush	Cervix	Severe	42	11	79	17	85	0.73 (0.36 to 1.48)	0.73 (0.36 to 1.48)	<0.50	—
		Mild	42	11	79	17	85	0.73 (0.36 to 1.48)			
Extended tip + Cytobrush	Cervix	Severe	42	11	79	17	85	0.73 (0.36 to 1.48)	0.73 (0.36 to 1.48)	<0.50	—
		Mild	42	11	79	17	85	0.73 (0.36 to 1.48)			
Extended tip + Cytobrush	Cervix	Severe	42	11	79	17	85	0.73 (0.36 to 1.48)	0.73 (0.36 to 1.48)	<0.50	—
		Mild	42	11	79	17	85	0.73 (0.36 to 1.48)			
Extended tip + Cytobrush	Cervix	Severe	42	11	79	17	85	0.73 (0.36 to 1.48)	0.73 (0.36 to 1.48)	<0.50	—
		Mild	42	11	79	17	85	0.73 (0.36 to 1.48)			
Extended tip + Cytobrush	Cervix	Severe	42	11	79	17	85	0.73 (0.36 to 1.48)	0.73 (0.36 to 1.48)	<0.50	—
		Mild	42	11	79	17	85	0.73 (0.36 to 1.48)			
Extended tip + Cytobrush	Cervix	Severe	42	11	79	17	85	0.73 (0.36 to 1.48)	0.73 (0.36 to 1.48)	<0.50	—
		Mild	42	11	79	17	85	0.73 (0.36 to 1.48)			
Extended tip + Cytobrush	Cervix	Severe	42	11	79	17	85	0.73 (0.36 to 1.48)	0.73 (0.36 to 1.48)	<0.50	—
		Mild	42	11	79	17	85	0.73 (0.36 to 1.48)			
Extended tip + Cytobrush	Cervix	Severe	42	11	79	17	85	0.73 (0.36 to 1.48)	0.73 (0.36 to		

Table 3—Sensitivity and positive predictive value of studies from which sufficient data were available

Method	Reference No	Cytology (+)	Histology (+)	Cytology (+) + histology (+)	Sensitivity (%)	95% Confidence interval	Positive predictive value (%)	95% Confidence interval
Mild dysplasia or worse (cytology) v CIN ≥I (histology)								
Ayre	26	—	55	44	80	67 to 90	—	—
	25	103	46	46	100	92 to 100	45	35 to 55
Extended tip + Cytobrush	35	82	78	62	80	69 to 88	76	65 to 84
Extended tip + cotton swab	35	81	88	61	69	59 to 79	75	64 to 84
Ayre + cotton swab	33	—	348	256	74	69 to 78	—	—
	25	128	122	111	90	84 to 95	87	79 to 92
Cotton swab	31	—	40	26	65	48 to 79	—	—
	25	113	122	99	81	74 to 88	88	80 to 93
Cytobrush	31	—	47	45	96	86 to 100	—	—
	33	—	348	191	55	50 to 60	—	—
Cervex	26	—	55	49	89	78 to 96	—	—
Mild dysplasia or worse (cytology) v CIN ≥III (histology)								
Ayre	51†	—	134	79	59	50 to 67	—	—
	25	103	58	52	90	79 to 96	50	41 to 60
Extended tip + Cytobrush	35	82	45	39	87	73 to 95	48	37 to 59
Extended tip + cotton swab	35	81	49	41	84	70 to 93	51	39 to 62
Ayre + cotton swab	25	128	58	55	95	86 to 99	43	34 to 52
Cotton swab	31	—	31	22	71	52 to 86	—	—
	25	113	58	51	88	77 to 95	45	36 to 55
Cytobrush	31	—	41	40	98	87 to 100	—	—
Extended tip	51†	—	131	92	70	62 to 78	—	—
Ayre + Cytobrush	51†	—	87	51	59	48 to 69	—	—
Multispatula	51†	—	82	52	63	52 to 74	—	—
Severe dysplasia or worse (cytology) v CIN ≥III (histology)								
Ayre	25	53	58	41	71	57 to 82	77	63 to 87
Ayre + cotton swab	25	61	58	43	74	61 to 85	70	57 to 80
Cotton swab	31	—	31	10	32	17 to 51	—	—
	25	40	58	30	52	38 to 65	75	58 to 87
Cytobrush	31	—	41	31	76	60 to 88	—	—

CIN = Cervical intraepithelial neoplasia.

†CIN≥II (histology) instead of CIN≥III.

For mild dysplasia or worse (cytological) versus at least grade III cervical intraepithelial neoplasia (histological) sensitivities were generally 85% or higher with positive predictive values of around 50%. Sensitivities were lower and positive predictive values higher in analyses using higher cut off points for cytological abnormality (table 3). To avoid drawing conclusions based on data that may not come from the same set of studies statistical pooling was not performed.

Discussion

Certain limitations should be borne in mind when considering this review. Important interobserver variation exists in cytotechnologists and pathologists.⁵²⁻⁵⁵ Hence in studies with only small numbers of smears cytological assessments are often done by one person. In large studies it may be difficult to adjust for this problem. In paired studies the sequence of assignment may influence results.⁵⁶⁻⁵⁷ Some researchers resolve this by changing the sequence continuously. Others place the technique of which they expect the best results in the position considered most disadvantageous. We fear that in some studies extended tip spatulas were reported as Ayre-type spatulas. Therefore, all relevant pooled relative risks were recalculated after combining data for Ayre-type spatulas and extended tip spatulas. This produced no substantial difference in the point estimate or significance of the original results.

Apart from sampling method, factors such as the training and experience of the sampler,⁵⁸ the day of the menstrual cycle, and the population studied may influence outcome. We, however, have no reason to think that such bias selectively favoured one device over another. Obtaining a second cervical sample immediately after the first—even with the same device—increases the yield of cytological abnormalities by almost one third.⁵⁹⁻⁶¹ This is

important when comparing the yield of two combined samples (for example, obtained with any spatula plus cotton swab or Cytobrush) with the yield from one sample only. Only one funnel plot provided evidence for publication bias. A substantial role of publication bias in this review therefore seems unlikely. The review comprised randomised and quasi-randomised studies only. However, repeating the analysis with the inclusion of cohort¹⁶⁻¹⁷ and pre-post studies¹⁵⁻¹⁸⁻²⁰ yielded closely similar results.

Taking into account the limitations several conclusions can be drawn. It is plainly not appropriate to sample with a Cytobrush, a cotton swab, or an Ayre spatula alone. In all comparisons they turned out to be worse, in many cases significantly so. Comparisons between a combination of spatula plus cotton swab or Cytobrush, an extended tip spatula, and the Cervex brush mostly showed no significant differences. This could result from a true similarity in diagnostic yield or from sample sizes that were too small to show statistically significant differences. Statistical power estimated for each comparison was high in some cases and very low in others. This suggests that for part of the comparisons additional research may be appropriate.

False positive results are unlikely to be selectively more frequent with any specific device. This is even less likely given the similar predictive values of the cytological results in relation to the histological results. We emphasise, however, that very small numbers of patients were included in these studies. In six studies sufficient histological data were available. All but one of these studies, however, comprised highly selected patients.

In summary, though some comparisons were based on small numbers, our findings support the advice to use either any spatula plus the Cytobrush or a cotton swab, a Cervex brush, or an extended tip spatula to obtain cervical smears. There is no sound evidence to support the use of other devices.

Key messages

- The yield of cytological abnormalities with two or more different sampling devices was compared in 29 randomised and quasi-randomised studies; in six studies enough histological data were available to calculate sensitivity or positive predictive value, or both
- The Ayre spatula, Cytobrush, or cotton swab alone generally performed significantly worse than the combination of a spatula and Cytobrush or cotton swab, the extended tip spatula, or the Cervex brush
- No substantial differences in sensitivity or positive predictive value were detected between the sampling methods
- Results support the use of either the extended tip spatula, the combination of any spatula plus Cytobrush or cotton swab, or the Cervex brush for cervical screening

A copy of all funnel plots may be obtained by writing direct to FB. We acknowledge the invaluable help of Berna Schouten for logistical work, André Knottnerus for commenting on a previous version of this paper, and Emmanuel Lesaffre for advice on power calculations.

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