Papers

Cross sectional study of conventional cervical smear, monolayer cytology, and human papillomavirus DNA testing for cervical cancer screening

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Abstract

Objectives To compare the sensitivity, specificity, and interobserver reliability of conventional cervical smear tests, monolayer cytology, and human papillomavirus testing for screening for cervical cancer.
Design Cross sectional study in which the three techniques were performed simultaneously with a reference standard (colposcopy and histology).
Setting Public university and private practices in France, with complete independence from the suppliers.
Participants 828 women referred for colposcopy because of previously detected cytological abnormalities and 1757 women attending for routine smears.
Main outcome measures Clinical readings and optimised interpretation (two blind readings followed, if necessary, by consensus). Sensitivity, specificity, and weighted κ computed for various thresholds of abnormalities.
Results Conventional cervical smear tests were more often satisfactory (91% *v* 87%) according to the Bethesda system, more reliable (weighted κ 0.70 *v* 0.57), and had consistently better sensitivity and specificity than monolayer cytology. These findings applied to clinical readings and optimised interpretations, low and high grade lesions, and populations with low and high incidence of abnormalities. Human papillomavirus testing associated with monolayer cytology, whether systematic or for atypical cells of undetermined significance, performed no better than conventional smear tests.
Conclusions Monolayer cytology is less reliable and more likely to give false positive and false negative results than conventional cervical smear tests for screening for cervical cancer.

Introduction

Liquid based "monolayer" cytology, possibly combined with human papillomavirus testing, is replacing conventional smear tests for cervical cancer screening in several countries (including the United States and Switzerland). However, there is substantial controversy about whether the new and costly technologies perform better than conventional cervical smear tests.[1 2] We previously compared the cost of monolayer cytology (ThinPrep, CYTYC; MA, USA) and human papillomavirus testing (Hybrid Capture II test, Digene; Gaithersburg, MD, USA) with conventional smear tests.[3] Here we assess the sensitivity and specificity of the three methods. We also examined the value of human papillomavirus testing in women with atypical squamous cells/glandular cells of undetermined significance (ASCUS/AGUS) and the interobserver reproducibility of the interpretation of conventional smears and monolayer cytology.

Methods

Full details of the study protocol have been published previously.[4] To avoid spectrum (case mix) bias[5] we considered two groups of consecutive women who were either referred for colposcopy because abnormalities had been detected on previous smears or were attending for routine smears at a French public university (n=2) and private practices (n=2). All procedures were carried out by skilled gynaecologists and experienced cytopathologists. Each woman underwent a standard conventional smear test. The remaining material was then used to prepare the monolayer slide and for human papillomavirus testing. To avoid work up bias, all women were evaluated by all three methods (conventional cervical smear tests, monolayer cytology, human papillomavirus testing) and by the reference method (colposcopy[6] followed by biopsy if abnormalities were detected). To avoid review and context biases[7] cytopathologists read the slides blind to the clinical context in addition to routine reading, separately and independently for the three methods. In cases of disagreement slides were read again to reach a consensus conclusion, given if necessary by an independent expert (optimised diagnosis). In a random sample of the women (30%) we assessed interobserver reproducibility of cytological diagnosis with readings blind to context.

Smear abnormalities were classified into five ordered categories (negative, ASCUS/AGUS, low

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bmj.com 2003;326:733

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grade (LSIL) or high grade (HSIL) squamous intraepithelial lesions, invasive cancer) and the reference standard into four ordered categories (normal colposcopy or negative biopsy result, cervical intraepithelial neoplasia (grades I, II, and III), invasive carcinoma[8]). We used optimised histological diagnoses for the reference standard. We carried out human papillomavirus testing using the cell suspension that remained after monolayer preparation[9] using low risk (types 6/11/42/43/44) and high risk (types 16/18/31/33/35/39/45/51/52/56/58/59/68) human papillomavirus probes.

Analysis

We compared the sensitivity, specificity, and proportions of unsatisfactory (according to the Bethesda system[8]) or limited slides using the two tailed MacNemar χ^2 test. The interobserver reproducibility of the readings was assessed with weighted κ statistics.[10]

To assess potential "sampling bias" due to the split sample technique (monolayer being sampled after conventional cervical smears) we repeated statistical analyses in the subsample of women in whom the residual material after monolayer cytology was sufficient for human papillomavirus testing. The results were similar to those for the whole group and are not shown.

Results

Between 1 September 1999 and 30 May 2000, 2585 women underwent investigation (table 1). Results of human papillomavirus testing were available from the 1785 women for whom there was enough residual material. The proportion of satisfactory slides was higher with conventional smear testing (91%) than with monolayer testing (87%), though the reasons for unsatisfactory or limited smears differed (table 2). Compared with conventional smear tests monolayer testing consistently showed more abnormalities (especially ASCUS/AGUS) (tables 3 and 4).

Conventional smear tests consistently had superior or equivalent sensitivity, specificity, and likelihood ratios than monolayer tests for the detection cervical intraepithelial neoplasia grade I or higher (table 5) and lesions ≥ grade II or higher (table 6). The sensitivity of systematic human papillomavirus DNA testing (high risk) was no higher than that of conventional smear testing and its specificity was much lower for both grades. For human papillomavirus testing only for ASCUS/AGUS, the sensitivity of the paired monolayer/human papillomavirus testing method was not significantly superior to cervical smear testing.

Interobserver agreement was good for conventional smears (weighted κ 0.69, 95% confidence interval 0.64 to 0.74) but only moderate for monolayers (0.57, 0.52 to 0.63) (table 7). The ASCUS/AGUS diagnosis with monolayer testing was especially unreliable.

Table 1 Characteristics of studied samples by population. Values are numbers (percentage) unless otherwise stated

	Women referred for colposcopy (n=828)	Women attending for routine smear (n=1757)
Mean (SD) age (years)	37.8 (11.6)	33.3 (11.1)
French	605 (73)	1579 (90)
Educational:		
No schooling or primary only	74 (9)	66 (4)
Secondary	472 (57)	927 (53)
Higher	276 (34)	757 (43)
Current smokers	337 (41)	542 (31)
Mean (SD) age at first intercourse (years)	18.5 (2.7)	18.4 (2.1)
Previous clinical pelvic inflammatory disease	13 (2)	12 (1)
Previous documented *Chlamydia trachomatis* infection	16 (2)	13 (1)
Mean (SD) No of pregnancies	2.0 (2)	1.2 (1.6)
Menopausal	119 (14)	144 (8)
First smear	0	220 (13)
Previous abnormal smears	828 (100)	68 (5)
Contraception:		
Combined oral contraceptive	368 (44)	913 (52)
Intrauterine device	90 (11)	176 (10)
Condoms	49 (6)	53 (3)
HIV positive	10 (1)	5 (0)
Centre:		
Hôpital Jean Verdier (public, Paris suburbs)	35 (4)	70 (4)
Hôpital Louis Mourier (public, Paris suburbs)	238 (29)	54 (3)
Laboratoire Cartier (private, Paris)	520 (63)	559 (32)
Centre d'Anatomie pathologique (private, Besançon)	35 (4)	1074 (61)
Results of colposcopy *:		
Normal	131 (16)	1405 (80)
Acetowhite epithelium	389 (47)	146 (8)
Iodine negative epithelium	665 (80)	322 (18)

*Acetowhite and iodine negative epithelium are not mutually exclusive so the total exceeds 100%.

Discussion

Our results support the superiority of conventional cervical smear testing, whether considered clinical readings or optimised interpretations, low or high grade lesions, or populations with a low or a high incidence of abnormalities. Human papillomavirus testing, systematic or for a diagnosis of ASCUS/AGUS testing, carried out with monolayer cytology was no better than conventional cervical smear testing. The greater reliability of the interpretation of conventional smears rather than monolayer smears is consistent with their better diagnostic or screening performance. Our findings disagree with those of most previous studies.

We ensured that we obtained the reference standard of colposcopy/histology for all women in the study, unlike previous studies that compared monolayer testing with conventional smear testing and that considered concordant positive and concordant negative tests as true positives and true negatives with discrepancies resolved by consensus review.[1 11–20] In these studies the proportion of verified cases varied between 0.1% and 30%, and the work up bias was substantial, artificially inflating sensitivity and mathematically favouring the test with the higher rate of false positives: the monolayer technique (or human papillomavirus testing). Two other studies either did not find any difference between the methods[21] or performed post hoc subgroup analyses.[22]

Limitations of study

In this study the cervical smear was prepared before the monolayer. However, a sampling bias favouring the conventional smear is unlikely as there were very few monolayer slides with only a few cells and the results were similar in the subgroup of women in whom human papillomavirus testing was still possible.[23] The rates of unsatisfactory and limited slides were low, which may be due to our selection of skilled physicians. The cytopathologists were also selected according to their interest in

reading smears: all had extensive experience in conventional smears and cervical biopsies, but their experience with monolayer cytology was initially limited. However, this bias was neutralised by the optimised interpretations in which the best assessment was obtained.

Implications

This study has implications for regulation of medical devices, clinical practice, and future research on screening for cervical cancer. Monolayer testing, which seems less reliable and less valid and is more expensive,[3] should not replace conventional smear tests for cervical cancer screening. Human papillomavirus testing as complementary to conventional smear testing should be further evaluated in clinical research.[24] Our results emphasise the need to improve the "hard evidence" in studies of new technologies for cervical screening by using adequate methodological standards.

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Funding: Direction Générale de la Santé and Programme Hospitalier de Recherche Clinique, French Ministry of Health

Table 2 Specimen adequacy and causes of inadequacy and limitation by method (clinical reading)*

	Conventional cervical smear (n=2582)*	Monolayer (n=2580)†
Satisfactory for evaluation	2343 (91%)	2241 (87%)‡
Satisfactory for evaluation but limited by§:	236	328
Cytolysis	6	19
Obscuring blood	36	25
Obscuring inflammation	79	44
Endocervical component absent	75	235
Scant squamous epithelial cells	3	4
Air drying artefacts	32	0
Staining problem	5	1
Unsatisfactory for evaluation:	3	11
Cytolysis	0	0
Obscuring blood	0	5
Obscuring inflammation	0	1
Endocervical component absent	0	0
Scant squamous epithelial cells	1	5
Air drying artefacts	2	0
Staining problem	0	0

*Data missing data for three.
†Data missing for five.
‡P<0.0001 for difference between groups (MacNemar χ^2 test).
§Causes of limited evaluation were not mutually exclusive.

Table 3 Interpretation of conventional cervical smear tests* or monolayer testing versus† reference standard (colposcopy and biopsy) by population

	Women referred for colposcopy					Women attending for routine smears				
Reference standard results	Normal	ASCUS/ AGUS	LSIL	HSIL	Invasive cancer	Normal	ASCUS/ AGUS	LSIL	HSIL	Invasive cancer
Conventional cervical smear (optimised interpretation)										
Normal colposcopy/ negative biopsy	231	26	25	7	0	1510	77	54	11	0
CIN grade I	30	21	157	37	0	22	11	22	6	0
CIN grades II-III	14	8	19	230	7	4	5	6	20	0
Invasive cancer	0	2	0	6	7	1	1	0	3	1
Monolayer (optimised interpretation)										
Normal colposcopy/ negative biopsy	220	24	35	9	0	1493	73	73	15	0
CIN grade I	37	23	158	25	0	22	9	18	12	0
CIN grades II-III	19	10	32	212	4	5	3	5	22	0
Invasive cancer	0	3	0	9	3	0	0	1	4	0
Conventional cervical smear (clinical reading)										
Normal colposcopy/ negative biopsy	175	31	63	21	0	1550	59	37	6	1
CIN grade I	18	20	173	33	0	23	8	24	6	0
CIN grades II-III	9	6	35	218	10	5	4	9	18	0
Invasive cancer	1	0	0	3	11	1	1	0	2	1
Monolayer (clinical reading)										
Normal colposcopy/ negative biopsy	166	34	59	27	0	1503	85	51	9	0
CIN grade I	29	29	157	30	0	26	9	15	11	0
CIN grades II-III	11	12	37	211	7	8	4	7	17	0
Invasive cancer	1	1	0	7	6	1	0	0	4	0

ASCUS/AGUS=atypical squamous cells/glandular cells of undetermined significance.
LSIL=low grade squamous intraepithelial lesions.
HSIL=high grade squamous intraepithelial lesions.
CIN=cervical intraepithelial neoplasia.
*Data missing for three to five conventional slides.
†Data missing for 11 monolayer slides

(AOM 98010); Association pour la Recherche sur le Cancer (9099). The guarantor accepts full responsibility for the conduct of the study, had access to the data, and controlled the decision to publish.

Competing interests: None declared.

Ethical approval: The approval of the ethics committee (Hôpital Cochin, Paris) for the study was obtained in July 1998.

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Table 4 Interpretation of conventional cervical smear testing* versus monolayer tests† by population

Result with conventional cervical smear test	Result with monolayer test									
	Women referred for colposcopy					Women attending for routine smears				
	Normal	ASCUS/AGUS	LSIL	HSIL	Invasive cancer	Normal	ASCUS/AGUS	LSIL	HSIL	Invasive cancer
Optimised interpretation										
Normal	229	19	17	7	0	1445	51	32	7	0
ASCUS/AGUS	19	17	16	3	0	48	21	15	9	0
LSIL	15	17	160	9	0	20	11	45	6	0
HSIL	12	7	32	227	2	4	2	5	29	0
Invasive cancer	0	0	0	9	5	0	0	0	1	0
Clinical reading										
Normal	147	17	26	9	0	1480	66	23	3	0
ASCUS/AGUS	24	14	18	1	0	39	20	9	4	0
LSIL	30	34	181	26	0	15	11	36	8	0
HSIL	6	9	28	230	2	1	1	5	25	0
Invasive cancer	0	1	0	9	11	1	0	0	1	0

ASCUS/AGUS=atypical squamous cells/glandular cells of undetermined significance. LSIL=low grade squamous intraepithelial lesions. HSIL=high grade squamous intraepithelial lesions.
*Data missing for three to five conventional slides.
†Data missing for 11 monolayer slides.

Table 5 Sensitivity, specificity, and likelihood ratios of conventional cervical smear testing, monolayer, and human papillomavirus (HPV) DNA testing for detection of cervical intraepithelial neoplasia grade I and above

Abnormality threshold	Colposcopy			Screening		
	Sensitivity(95% CI)	Specificity(95% CI)	Likelihood ratio+/ likelihood ratio–	Sensitivity(95% CI)	Specificity(95% CI)	Likelihood ratio+/ likelihood ratio–
≥ASCUS/AGUS*						
Cervical smear (clinical reading)	95 (93 to 97)	60 (55 to 66)	2.39/0.09	72 (63 to 80)	94 (93 to 95)	11.49/0.30
Monolayer (clinical reading)	92 (90 to 95)	58 (52 to 64)	2.19/0.13	66 (56 to 75)	91 (90 to 93)	7.47/0.38
Cervical smear (optimised interpretation)	92 (90 to 94)	80 (75 to 85)	4.58/0.10	74 (66 to 83)	91 (90 to 93)	8.64/0.28
Monolayer (optimised interpretation)	90 (87 to 92)	76 (71 to 81)	3.79/0.14	73 (65 to 82)	90 (89 to 92)	7.53/0.30
≥Low grade squamous intraepithelial lesions†						
Cervical smear (clinical reading)	90 (87 to 92)	71 (66 to 76)	3.11/0.14	59 (49 to 68)	97 (97 to 98)	22.10/0.42
Monolayer (clinical reading)	85 (82 to 88)	70 (65 to 75)	2.81/0.22	53 (43 to 63)	96 (95 to 97)	14.54/0.49
Cervical smear (optimised interpretation)	86 (83 to 89)	89 (85 to 93)	7.77/0.16	57 (48 to 67)	96 (95 to 97)	14.59/0.44
Monolayer (optimised interpretation)	83 (80 to 86)	85 (81 to 89)	5.42/0.20	61 (52 to 71)	95 (94 to 96)	11.54/0.41
RLU/cut-off value ratio >1.0‡						
HPV DNA (high risk types)	79 (74 to 83)	77 (71 to 83)	3.46/0.28	64 (53 to 76)	86 (85 to 88)	4.73/0.41
HPV DNA (high and low risk types)	82 (77 to 86)	74 (67 to 80)	3.13/0.25	69 (58 to 79)	83 (81 to 85)	4.09/0.38
≥Low grade squamous intraepithelial lesions or RLU/cut-off value ratio >1.0 if ASCUS/AGUS¶						
Monolayer (clinical reading) or HPV DNA (high risk types) if ASCUS/AGUS	87 (83 to 91)	66 (58 to 73)	2.41/0.20	59 (47 to 70)	96 (95 to 97)	13.50/0.43
Monolayer (optimised interpretation) or HPV DNA (high risk types) if ASCUS/AGUS	85 (80 to 89)	82 (76 to 88)	4.75/0.19	67 (56 to 78)	94 (92 to 95)	10.86/0.35

*Clinical reading: conventional smear superior to monolayer for both sensitivity (p<0.05) and specificity (P<0.001). Optimised interpretation: conventional smear superior to monolayer for specificity (P<0.05) but not for sensitivity (P=0.07).
†Clinical reading: conventional smear superior to monolayer for sensitivity (P<0.001) but not for specificity (P=0.07). Optimised interpretation: conventional smear superior to monolayer for specificity (P<0.001) but not for sensitivity (P=0.08).
‡HPV results expressed as relative light units (RLUs), which represent ratio of light emission of sample to average of three positive controls provided by manufacturer, containing 1 pg/ml HPV 16 DAN. RLU ≥1, corresponding to ≥5000 HPV-DNA copies per test well, was considered to be positive.
§Sensitivity and specificity of HPV DNA testing (high risk types) lower (P<0.0001) than both cytological techniques.
¶Clinical reading: paired monolayers/HPV testing superior but not significantly to standard conventional smear for sensitivity (P=0.88) and inferior for specificity (P<0.001). Optimised interpretation: paired monolayers/HPV testing superior but not significantly to standard conventional smear for sensitivity (P=0.06) and inferior for specificity (P<0.001).

Table 6 Sensitivity, specificity, and likelihood ratios of conventional cervical smear testing, monolayer, and human papillomavirus (HPV) DNA testing for detection of cervical intraepithelial neoplasia grade II and above

	Colposcopy			Screening		
Abnormality threshold	**Sensitivity(95% CI)**	**Specificity(95% CI)**	**Likelihood ratio+/ likelihood ratio–**	**Sensitivity(95% CI)**	**Specificity (95% CI)**	**Likelihood ratio+/ likelihood ratio–**
≥High grade squamous intraepithelial lesions *						
Cervical smear (clinical reading)	83 (78 to 87)	90 (87 to 92)	8.17/0.19	51 (36 to 67)	99(99 to 100)	67.53/0.49
Monolayer (clinical reading)	79 (74 to 84)	89 (87 to 92)	7.34/0.24	51 (36 to 67)	99 (98 to 99)	43.25/0.49
Cervical smear (optimised interpretation)	85 (81 to 89)	92 (89 to 94)	10.36/0.16	60 (45 to 75)	99(99 to 99)	60.46/0.40
Monolayer (optimised interpretation)	78 (73 to 83)	94 (92 to 96)	12.19/0.23	65 (50 to 80)	98 (98 to 99)	41.29/0.36
RLU/cut-off value ratio >1.0†						
HPV DNA (high risk types)	80 (74 to 86)	54 (49 to 60)	1.75/0.37	96 (88 to 100)	85 (83 to 87)	6.52/0.05
HPV DNA (high and low risk types)	81 (75 to 87)	50 (44 to 55)	1.60/0.39	96 (88 to 100)	82 (80 to 84)	5.32/0.05
≥High grade squamous intraepithelial lesions or RLU/cut-off value ratio >1.0 if ASCUS/AGUS‡						
Monolayer (clinical reading) or HPV DNA (high risk types) if ASCUS/AGUS	82 (76 to 88)	86 (82 to 90)	5.94/0.21	64 (45 to 83)	98 (97 to 99)	28.47/0.37
‡Monolayer (optimised interpretation) or HPV DNA (high risk types) if ASCUS/AGUS	80 (74 to 86)	93 (90 to 96)	11.60/0.21	76 (59 to 93)	97(97 to 98)	29.71/0.25

*Clinical reading: conventional smear is superior to monolayer but not significantly for both sensitivity (P=0.12) and specificity (P=0.16). Optimised interpretation: conventional smear is superior to monolayer for sensitivity (P<0.001) but not for specificity (P=1.00).
†Sensitivity of HPV DNA testing (high risk types) is higher but not significantly than that of conventional smear (P=0.66) but specificity is lower (P<0.0001).
‡Clinical reading: paired monolayers/HPV testing is superior but not significantly to standard conventional smear for sensitivity (P=0.29) but inferior for specificity (P<0.001). Optimised interpretation: paired monolayers/HPV testing is superior but not significantly to standard conventional smear for sensitivity (P=0.73) but inferior for specificity (P<0.001).

What is already known on this topic

New technologies have been developed to improve the detection of cervical cancer and its precursors and reduce the rate of false negative results from conventional cervical smear tests

In several countries liquid based monolayer cytology is replacing conventional smear tests, despite controversy about whether these more expensive tests perform better

What this study adds

Conventional cervical smear testing is superior in terms of low and high grade lesions and in populations with a low or a high incidence of abnormalities

Monolayer testing is less reliable and should not replace conventional cervical smear testing

Table 7 Interobserver reliability for conventional smear tests and monolayer tests*

	Second interpretation				
First interpretation	**Normal**	**ASCUS/AGUS**	**LSIL**	**HSIL**	**Invasive cancer**
Cervical smear					
Normal	448	35	15	13	0
ASCUS/AGUS	13	25	14	4	0
LSIL	34	11	33	8	0
HSIL	6	4	4	86	0
Invasive cancer	0	0	0	0	8
Monolayer cytology					
Normal	442	33	14	8	0
ASCUS/AGUS	29	11	10	6	0
LSIL	48	10	28	10	0
HSIL	16	10	22	65	0
Invasive cancer	0	0	0	0	2

*Data available (two blinded interpretations) for 761 conventional smear slides and 764 monolayer slides.

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(Accepted 29 January 2003)