

Articles

Management of women who test positive for high-risk types of human papillomavirus: the HART study

J Cuzick, A Szarewski, H Cubie, G Hulman, H Kitchener, D Luesley, E McGoogan, U Menon, G Terry, R Edwards, C Brooks, M Desai, C Gie, L Ho, I Jacobs, C Pickles, P Sasieni

Summary

Background Certain types of human papillomavirus (HPV) are the primary cause of almost all cervical cancers. HPV testing of cervical smears is more sensitive but less specific than cytology for detecting high-grade cervical intraepithelial neoplasia (CIN2+). HPV testing as a primary screening approach requires efficient management of HPV-positive women with negative or borderline cytology. We aimed to compare the detection rate and positive predictive values of HPV assay with cytology and to determine the best management strategy for HPV-positive women.

Methods We did a multicentre screening study of 11 085 women aged 30–60 years. Women with borderline cytology and women positive for high-risk HPV with negative cytology were randomised to immediate colposcopy or to surveillance by repeat HPV testing, cytology, and colposcopy at 12 months.

Findings HPV testing was more sensitive than borderline or worse cytology (97.1% vs 76.6%, $p=0.002$) but less specific (93.3% vs 95.8%, $p<0.0001$) for detecting CIN2+. Of 825 randomised women, surveillance at 12 months was as effective as immediate colposcopy. In women positive for HPV at baseline, who had surveillance, 73 (45%) of 164 women with negative cytology and eight (35%) of 23 women with borderline cytology were HPV negative at 6–12 months. No CIN2+ was found in these women, nor in women with an initial negative HPV test with borderline ($n=211$) or mild (32) cytology.

Interpretation HPV testing could be used for primary screening in women older than 30 years, with cytology used to triage HPV-positive women. HPV-positive women with normal or borderline cytology (about 6% of screened women) could be managed by repeat testing after 12 months. This

approach could potentially improve detection rates of CIN2+ without increasing the colposcopy referral rate.

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See Commentary

Introduction

Certain types of the human papillomavirus (HPV) are the primary cause of almost all cases of cervical cancer.^{1–3} DNA tests can detect high-risk types of HPV in cells obtained during routine cytological screening. Results of several studies have highlighted the lack of sensitivity of routine cytology and indicated that HPV testing has a high sensitivity (around 95%) for identifying high-grade cervical intraepithelial neoplasia (CIN2/3) or glandular neoplasia.^{2,4–12} Development of invasive cancer after an apparently normal smear is increasingly common.¹³ However, HPV testing also identifies many transient HPV infections that are not associated with high-grade CIN, which reduces the test's specificity. For HPV testing to be cost effective in primary screening, it would be necessary to develop an efficient policy for the management of women who test positive for high-risk HPV types, but who have negative cytology or minimal (borderline) cytological changes. Such a strategy would provide a basis for a new approach to cervical screening in which the primary screening test would be for HPV alone, and cytology would be reserved for the triage of women with positive HPV test results.

The HART (HPV in Addition to Routine Testing) study was designed to investigate this approach, with particular emphasis on the management of HPV-positive women with borderline or negative cytology; to estimate the sensitivity and specificity of HPV testing; and to establish the appropriate management of women with borderline or low-grade cytological abnormalities, for which the specificity of cytology is poor. The specific aims of the study were to compare the detection rate and positive predictive value of semiquantitative HPV assays with conventional cytology; assess the importance of viral persistence in reducing false-positive results from HPV testing; and determine the appropriate recall interval for women with borderline smears that are either HPV positive or negative, and for women with negative cytology but positive HPV test results.

Methods

Participants and procedures

Women were recruited from 161 family practices in the UK associated with five referral centres in Birmingham, Edinburgh, London, Manchester, and Mansfield. Women aged 30–60 years attending for routine cervical screening were eligible, provided they had not had an abnormal smear in the past 3 years and had never been treated for CIN.

On screening, in addition to conventional cytology (taken with an extended-tip spatula), a second sample was

Cancer Research UK, London, UK (Prof J Cuzick PhD, A Szarewski MFFP, G Terry PhD, R Edwards PhD, C Brooks MSc, L Ho MD, P Sasieni PhD); **Royal Infirmary of Edinburgh, Edinburgh, UK** (H Cubie FRCPath, E McGoogan FRCPath); **City Hospital, Nottingham, UK** (G Hulman FRCPath); **St Mary's Hospital, Manchester, UK** (Prof H Kitchener FRCOG); **Women's Hospital, Birmingham, UK** (Prof D Luesley FRCOG); **University Medical School, Edinburgh** (E McGoogan); **Queen Mary's School of Medicine and Dentistry, London** (Prof J Cuzick, U Menon MRCOG, G Terry, L Ho, Prof I Jacobs MRCOG, Prof P Sasieni); **Christie Hospital, Manchester** (M Desai MRCPATH); **and The King's Mill Centre, Sutton-in-Ashfield, UK** (C Gie FRCOG, C Pickles MRCOG)

Correspondence to: Prof J Cuzick, Cancer Research UK, Department of Epidemiology, Mathematics, and Statistics, Wolfson Institute of Preventive Medicine, Queen Mary's School of Medicine and Dentistry, Charterhouse Square, London EC1M 6BQ, UK (e-mail: jack.cuzick@cancer.org.uk)

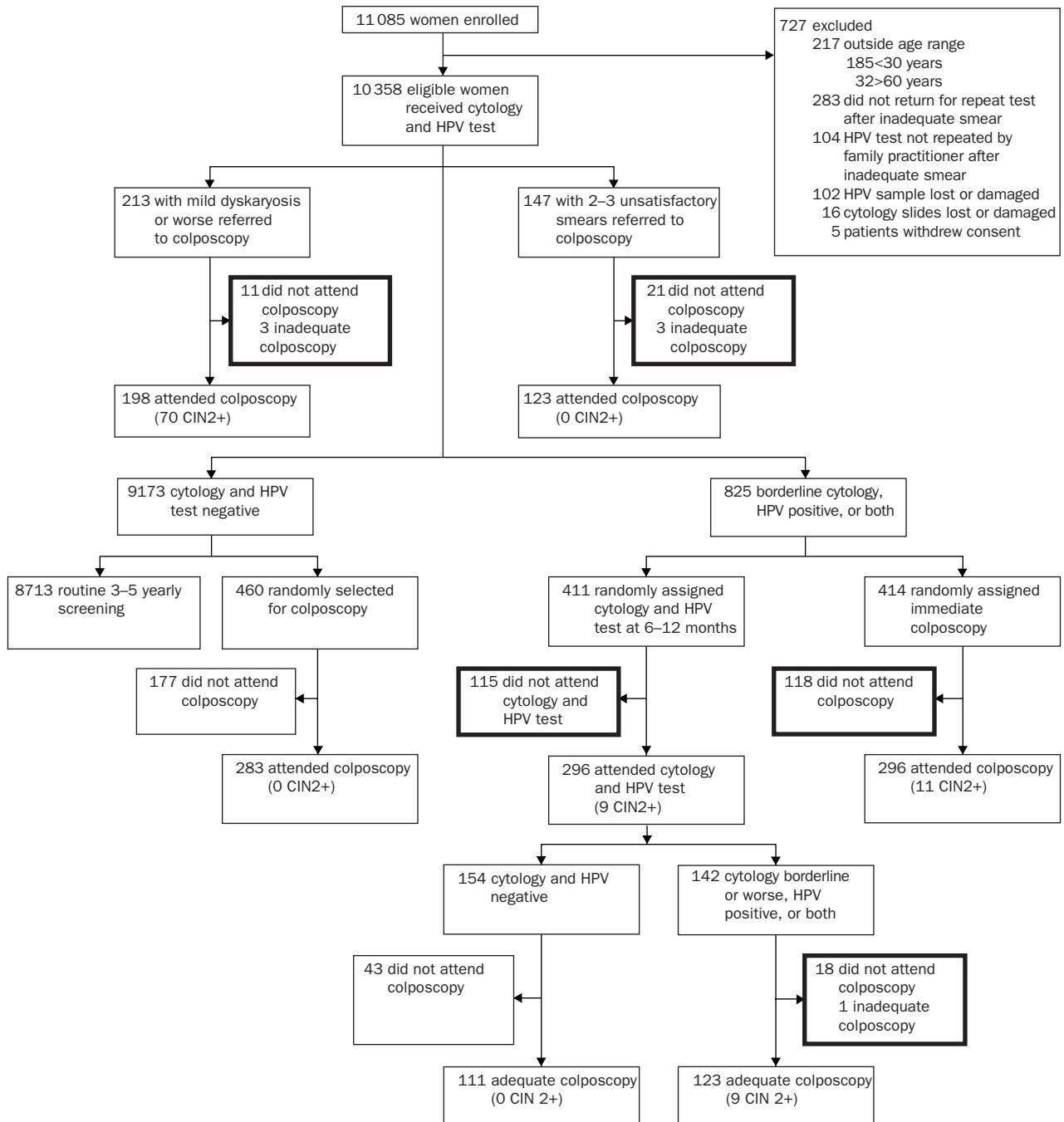


Figure 1: **Trial profile**

Inadequate colposcopy = women for whom no adequate biopsy sample was obtained. Boxes with bold outline contain women with incomplete assessment for CIN2+.

taken from the cervix using a cone-shaped cervical sampler brush (Digene, Gaithersburg, MD, USA) and placed into standard transport medium for transport to one of two laboratories.

Figure 1 shows the trial profile. Women with a cytological diagnosis of mild dyskaryosis or worse were referred for immediate colposcopy. We defined women with borderline cytology, or positive high-risk HPV test results and negative cytology, as the minimal abnormality group. Once test results were known, these women were randomised to immediate colposcopy or to surveillance by HPV testing and cytology at 6 and 12 months. Randomisation was done centrally by block randomi-

sation of size 8 with no stratification by centre. Women in the surveillance group were referred to colposcopy at 6 months if the cytology result progressed to mild dyskaryosis or worse. In all other cases they were invited for colposcopy and repeat testing at 12 months.

To estimate sensitivities, specificities, and positive-predictive values, we obtained reviewed histological evidence of CIN2, CIN3, microinvasion, adenocarcinoma in situ, invasive adenocarcinoma, or invasive cancer for a positive disease classification (defined as CIN2+). There was one case of CIN2 in which the biopsy was not available for review, which we included. Women with no worse than CIN1 on reviewed histology

were classed as negative for CIN2+ as were those with negative colposcopy and no biopsy results. Women testing negative on both HPV and cytology either initially or, in the surveillance group, on follow-up were also classed as CIN2+ negative. Disease classification was treated as missing in women with incomplete assessment (n=290)

To assess the absolute sensitivity of both tests we assessed the rate of false-negative results by inviting a random 5% sample (chosen from blocks of size 100 with stratification by centre) of women in whom both tests were initially negative for colposcopy. Colposcopy was done in hospital gynaecology clinics according to NHS Cervical Screening Programme (NHSCSP) guidelines in which the recommendation is to do a biopsy of any abnormality.¹⁴ Women who had two consecutive unsatisfactory cytological tests (or three in Edinburgh) were also referred for colposcopy, irrespective of HPV result. These women were excluded from the analyses of cytology. Women who did not attend for colposcopy were offered at least two additional appointments, and in most cases were also reminded of their appointment by telephone. After the patient had failed to attend on three occasions, the patient's family practitioner was informed, and the woman was recorded as having defaulted. If available, results of biopsies done outside of the study in defaulting women were added to the study database.

All cytological results were based on routine reports from the five participating centres. Colposcopists had access to patients' notes including cytology results, but were not given HPV results. However, they may have been able to guess the HPV result in some cases—eg, cytology negative, HPV positive—because the results affected management. Histology was read locally, but was reviewed centrally in a blinded fashion by one pathologist. A panel of pathologists reviewed a sample of discrepant slides; the initial review diagnosis was used in all cases because these results agreed closely with those of the review panel ($\kappa=0.92$; κ exceeded 0.81 in 97.5% of 5000 bootstrap replications).

Women were given a study information leaflet and after discussion with their doctor or nurse were invited to join the study. Written informed consent was obtained in all cases. The study was approved by a multicentre research ethics committee and by local committees at all five centres.

HPV testing

HPV testing was done in one of two laboratories using hybrid capture II (Digene, Gaithersburg, MD, USA) with only the high-risk group of probes. These probes are designed to detect HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. The tests were done according to the manufacturers' instructions and results given as the ratio of the relative light units (RLU) given by the test specimen to that given by a 1 pg/mL HPV DNA control (RLU for a 1 pg cut-off). Before the start of the study, both laboratories completed the manufacturers' proficiency test and obtained very similar results on test samples. Similar overall results were obtained from both laboratories.

Statistical analyses

We calculated that 12 000 women should be enrolled to ensure that at least 900 (7.5%) were in the minimal abnormality group. Assuming 70% compliance, this sample size gave more than 90% power to detect a reduction in false-positive referrals (ie, women who did not have high-grade CIN) from 80% to 70%.

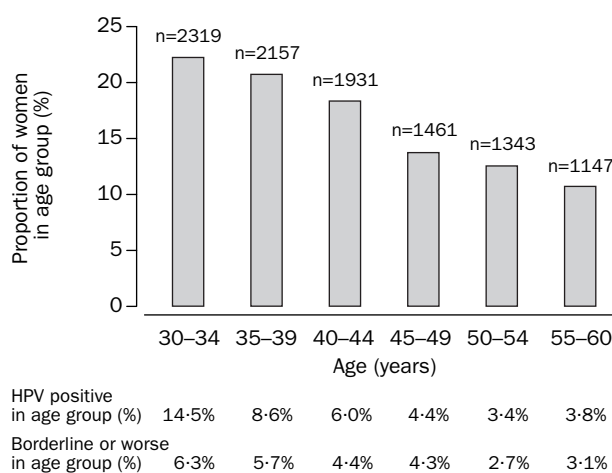


Figure 2: Age distribution at study entry, and rates of positive results for cytology and HPV tests

Results are for the 10 358 eligible women enrolled.

Most results are presented as percentages with 95% CIs. Women were stratified by baseline cytology, HPV results, and randomisation group. To correct for differential attendance for colposcopy (incomplete assessment), sensitivity, specificity, and positive-predictive values were adjusted for differential non-compliance between strata. Specifically, the disease rates were calculated within each stratum for women with adequate follow-up and applied to the whole stratum. Confidence intervals were calculated with methods appropriate for survey data (Stata statistical software, release 8.0). No CIN of any stage was found in the small sample of double negatives that had colposcopy. Nevertheless, it is not possible to confidently rule out any disease in this group, and sensitivities are best considered as relative sensitivities, which are appropriate for comparing different tests and strategies. Comparisons between performance characteristics of cytology and HPV testing were made with bootstrap methods. p values for these differences were twice the one-sided p value based on 20 000 replications.

Role of the funding source

The sponsor (Cancer Research UK) and the commercial partner (Digene Corporation) had no role in study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to publish the article.

Results

11 085 unselected women attending for routine screening were enrolled from 161 family practices referring to five centres between August, 1998 and November, 2001 (figure 1). Of these, 727 were ineligible or could not be assessed (figure 1). Our analyses are based on the remaining 10 358 women, of whom 825 (8.0%) were in the minimal abnormality group. We stopped recruitment early since rates were slowing and the power of the study was only slightly reduced.

Mean age was 42 years (SD 8.6); the age distribution (figure 2) within the 30–60 year age limit was very similar to the distribution in the English screening programme,¹⁵ in which younger and older women are also included. 213 women (2.1%) had an initial cytological diagnosis of mild dyskaryosis or worse and were immediately referred for colposcopy. The age-specific rates of this initial diagnosis were 25% lower than in the English programme.¹⁵

	Baseline cytology (n[% HPV positive])							Total n
	Unsatisfactory on 2 smears	Normal	Borderline	Mild dyskaryosis	Moderate dyskaryosis	Severe dyskaryosis	? Glandular	
Histological outcome								
No colposcopy	22 (5%)	9107 (2%)	77 (29%)	10 (100%)	1 (100%)	0	0	9217
Colposcopy but no histology	8 (0%)	12 (58%)	5 (40%)	4 (50%)	0	0	1 (0%)*	30
Normal	106 (8%)	551 (51%)	185 (21%)	72 (65%)	18 (56%)	5 (80%)	1 (0%)	938
Borderline/HPV/CIN1	11 (9%)	24 (33%)	17 (59%)	24 (79%)	1 (100%)	6 (83%)	0	83
CIN2	0	3 (100%)	1 (100%)	6 (100%)	10 (100%)	0	1 (0%)†	21
CIN3	0	12 (100%)	4 (100%)	6 (100%)	13 (92%)	27 (96%)	1 (100%)	63
Invasive	0	0	0	0	0	2 (100%)	1 (100%)	3
Adenocarcinoma in situ	0	0	0	0	0	1 (100%)	2 (100%)	3
Total	147 (7%)	9709 (6%)	289 (27%)	122 (74%)	43 (79%)	41 (93%)	7 (57%)	10 358

? Glandular indicates smears suggestive of glandular carcinoma of the cervix. *Biopsy taken but unsatisfactory. †Based on local histology result (material was unavailable for review).

Table 1: Baseline cytology, HPV results, and reviewed histological outcome for all eligible patients

414 women were randomised to immediate colposcopy and 411 to surveillance (figure 1). In the 5% sample of women in whom both tests were negative, 283 (62%) of 460 attended colposcopy (figure 1). No CIN of any grade was detected in this group or in the 147 women who had repeatedly unsatisfactory smears. In total, the first smear was inadequate in 10% of women. All undamaged samples received by the laboratories were adequate for HPV testing. 102 HPV samples were lost or damaged (figure 1), most during postage to the central laboratories, which would not occur in routine screening.

Cytology, HPV, and histological results are summarised in table 1. Overall, 90 women had high-grade CIN on reviewed histology. Test results for these 90 cases are compared in table 2. If positive cytology was classed as mild dyskaryosis or worse, cytology had a sensitivity of 70.1%, specificity of 98.6%, and positive predictive value of 34.0%. Sensitivity increased to 76.6% if borderline dyskaryotic smears were treated as positive, but specificity dropped to 95.8% and predictive value to 15.8%. Borderline smears were fairly common (2.8%), but had a predictive value of only 3.3% (four of 123 women randomised to immediate colposcopy who were fully assessed), compared with 10.7% (12 of 112) for mild dyskaryosis and 64% (58 of 90) for moderate and severe squamous abnormalities and glandular abnormalities (tables 1 and 4).

HPV testing was more sensitive than cytology (97.1% vs 76.6% respectively; $p=0.002$) but was less specific (93.3% vs 95.8%, respectively; $p<0.0001$), and had predictive value of 12.8%, which was similar to that for a borderline or worse smear (15.8%). Higher levels of HPV were more likely to be associated with CIN2+ (table 3), and a cut-off equivalent to 2 pg/mL gave a slightly better predictive value (15.0%) with little loss of sensitivity.

Test	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)
Cytology \geq borderline	76.6 (65.1–85.1)	95.8 (95.4–96.2)	15.8 (12.7–19.4)
Cytology \geq mild	70.1 (58.7–79.5)	98.6 (98.4–98.8)	34.0 (27.8–40.7)
HPV \geq 1 pg	97.1 (91.2–99.1)	93.3 (92.7–93.9)	12.8 (10.4–15.7)
HPV \geq 2 pg	96.0 (89.7–98.5)	94.4 (93.9–95.0)	15.0 (12.2–18.34)
Cytology \geq mild or HPV \geq 2 pg	100 (96.0–100)*	94.0 (93.4–94.5)	14.4 (11.8–17.5)

Results are based on 90 cases of CIN2+ with reviewed histology. *97.5% one-sided CI. With full compliance we estimated that there would have been 107.7 high grade lesions (17.7 extra in those not complying) of which 3.1 would have been missed by HPV, 25.7 by cytology at a borderline cut off and 32.4 with a mild cut off.

Table 2: Performance characteristics for CIN2+ for cytology and HPV testing

However, weakly positive HPV tests were rare—only 2.0% were between 1 and 4 RLU.

The key results for women with minimal abnormalities are shown in table 4. There were 11 high-grade lesions in the immediate colposcopy group compared with nine in the surveillance group, indicating that high-grade lesions rarely regress over a 12-month period. All 20 women with high-grade lesions in the minimal abnormality group tested HPV positive at baseline. No invasive cancers were detected, suggesting that it is safe to monitor these women by yearly surveillance. Low-grade lesions were significantly lower in the surveillance than immediate colposcopy group (31 vs 16, respectively, $p=0.04$), reinforcing the high regression rate of low-grade lesions and the benefit of surveillance. Additionally, all high-grade lesions in women with borderline cytology were strongly HPV positive at baseline, and there was no high-grade disease in the 178 women with borderline cytology who were HPV negative (97.5% one-sided CI for rate of CIN2+ in this group 0–2.1%). This result suggests that women with borderline cytology whose HPV tests were negative (73% of borderline lesions) could have been safely returned to routine 3–5 yearly screening without additional follow-up. Furthermore, in all nine women with high-grade lesions under surveillance, HPV tests remained positive at follow-up (table 5). 90 (74%) of 122 women with mild dyskaryosis were HPV positive. All twelve women in this group with CIN2+ were HPV positive.

Figure 2 shows the age-specific proportions of HPV-positive results. Combining these data with the age distribution of women screened in England¹⁵ yields an age-standardised HPV-positive rate of 8.8%.

Of the 780 women with a positive HPV test result and an adequate smear, the smear result was negative in 536

Histological outcome	n per baseline HPV category (RLU)						Total
	<0.3	0.3–0.99	1.0–1.99	2.0–3.99	4.0–9.99	\geq 10	
No colposcopy	7904	1065	35	37	26	150	9217
Colposcopy abnormal but no histology	17	2	1	2	1	7	30
Normal	486	66	71	49	57	209	938
Borderline/HPV/CIN1	25	6	1	5	2	44	83
CIN2	1*	0	0	0	2	18	21
CIN3+	0	2	1	3	1	62	69
Total	8433	1141	109	96	89	490	10 358

RLU=relative light unit. *Based on local histology result (material was unavailable for review).

Table 3: Baseline HPV values and histological outcome for all eligible patients

	Smear bord HPV neg (n)	Smear bord HPV pos (n)	Smear neg HPV pos (n)	Total n (%)
Immediate colposcopy group (n=414)				
No follow-up	15	7	96	118 (29%)
Normal	83	18	153	254 (61%)
Low-grade	8	10	13	31 (7%)
High-grade	0	4	7	11 (3%)
Total	106	39	269	414
Surveillance group (n=411)				
No follow-up	18	9	88	115 (28%)
Normal*	85	26	160	271 (66%)
Low-grade*	2	3	11	16 (4%)
High-grade	0	1	8	9 (2%)
Total	105	39	267	411

Bord=borderline. Neg=negative. Pos=positive. *Based on follow-up cytological data if patient did not attend colposcopy.

Table 4: **Main outcomes for women with minimal screening abnormalities**

(69%), borderline in 78 (10%), and mildly dyskaryotic or worse in 166 (21%). Table 6 shows the results of tests at 6–12 months' follow-up in the surveillance group in women with negative or borderline cytology. Regression of HPV (positive becoming negative) within 6–12 months occurred in 45% of women who were initially negative on cytology, and 35% of women initially borderline on cytology.

Discussion

Our results show that HPV testing for a group of high-risk virus types is a more sensitive primary screening technique than cytology for detecting high-grade CIN, confirming the findings of other studies.^{2,4-12} Therefore, use of HPV testing in addition to cytology would improve the detection rate of high-grade CIN and should prevent more cancers than use of cytology alone. An impediment to use of HPV testing in primary screening is the high rate of positive results in women who do not have significant histological abnormalities. Our results suggest that HPV testing not only improves detection rates, but also, if used appropriately, could safely reduce colposcopy referral rates.¹⁶ Reduction of referral rates can only be achieved if the very high negative predictive value of HPV infection is used to: return women who test negative for HPV, with borderline cytology, to routine screening; retest HPV-positive women with negative or borderline cytology after 12 months; and extend the screening interval from 3 to 5 years.

Also, HPV testing is more sensitive than cytology in the triage of women with ASCUS (atypical squamous cells of undetermined significance) smears.^{17,18} Additionally, HPV testing might have a role in reducing the referral rate for women with mild dyskaryosis, by immediately referring to colposcopy only women positive for high-risk types of HPV, and allowing a 6–12-month retesting strategy for women who test negative for HPV. In the surveillance group of our study, 105 women with borderline smears had negative HPV tests, as did 32 women with mildly dyskaryotic smears. This result must be balanced against around 150 women (56% of 267, table 5) whose cytology was

Histological outcome	Initial and follow-up HPV result category (n)						Total (n)
	-/-	-/+	-/X	+/-	+/+	+/X	
Normal	78	4	3	82	97	7	271
Low-grade	2	0	0	2	11	1	16
High-grade	0	0	0	0	9	0	9
No follow-up	0	0	18	0	0	97	115
Total	80	4	21	84	117	105	411

--indicates HPV negative, +=HPV positive (≥ 1 RLU), X=no sample.

Table 5: **Persistence of HPV in women in surveillance group (n=411)**

	Initial cytology and HPV results		
	Cytology negative + HPV positive	Cytology borderline + HPV positive	Cytology borderline + HPV negative
Results at 6–12 months			
Both tests negative	61	7	55
Cytology negative + HPV positive	67	1	1
Cytology borderline + HPV negative	5	0	16
Cytology borderline + HPV positive	18	6	2
Cytology mild + HPV negative	1	1	4
Cytology mild + HPV positive	12	8	1
Total	164	23	79

*30 women had inadequate tests.

Table 6: **Initial and follow-up cytology and HPV results in women in surveillance group who attended follow-up and had adequate cytology and HPV tests (n=296)***

negative but whose HPV tests were positive at baseline and who would have been referred to colposcopy 6–12 months later (assuming all women return for a second test). Thus, the referral rate for every screening round would be similar, but a longer interval between tests would lead to fewer overall referrals. Some of these issues are being investigated by the NHS in three pilot sites.

Issues of acceptability and compliance with follow-up will be important if the test is to be introduced routinely. The use of HPV testing reinforces the fact that cervical cancer is caused by a sexually transmitted virus, and it will be essential for the test result and its implications to be communicated sensitively. However, the patient or her partner could have been infected many years previously. We did not attempt to recruit on a population basis, but involved only certain nurses in family practices that were prepared to be involved, so we are unable to make precise statements about the acceptability of the test. The fact that our abnormality rate was 25% lower than the national average might also limit the general applicability of our results, but there is considerable variation in rates, with 20% of laboratories having rates lower than those noted in this study. Additionally, the published rates refer to all primary-care smears, whereas we excluded women with a recent abnormal smear and women who had been previously treated—groups in whom abnormality rates would be higher. Compliance for follow-up in randomised women was only 71% in the immediate colposcopy group and 72% in the surveillance group (table 4). These rates might have been partly caused by the fact that in some centres, the local ethics committee did not allow us to tell a woman that her HPV test was positive, but a high compliance for retesting in women who are HPV positive but are cytologically negative or have only borderline changes is clearly important.

Our results can be translated to centres using the Bethesda system of classification, since borderline smears are similar to ASCUS, except when koilocytosis is present, when they are called LSIL (low-grade squamous intraepithelial lesions). Mild dyskaryosis is also similar to LSIL, although LSIL might include some smears read as moderate dyskaryosis in the UK.¹⁹

Rather than adding HPV testing to cytology, it might be more cost effective to use HPV testing as the primary screening test, reserving cytology for women who test positive.²⁰ However, several issues would need to be addressed: cost, widespread dissemination of information about HPV, and the appropriate screening algorithm for

women younger than 30 years. Costs of HPV testing are currently substantially higher than for cytology, but are certain to drop for high volume use in primary screening. Also, costs are at least balanced, and potentially reduced, if HPV testing can safely permit longer screening intervals.^{16,21-23}

Our results do not provide direct evidence that use of HPV testing will reduce cancer rates. The high detection rate suggests that cancer rates would fall, but a very large, probably cluster randomised trial is necessary to definitively establish such a benefit. A limitation of our trial is its concurrent design, in which all women received both tests. Such a design is efficient for comparing sensitivity and positive predictive values, but cannot be used directly to assess effects on cancer rates. Also, we took a second sample for HPV after the cytology specimen was obtained, whereas it is most likely that one liquid-based sample would be taken for both tests in the future. This approach will provide a more adequate sample, which might lead to slightly better results for cytology, but is unlikely to affect HPV test results.²⁴ A trial in which conventional screening and management is compared with primary HPV testing and cytology triage should be a high priority. The duration of low risk after a negative HPV test result is not known but is being investigated by extended follow-up of previous and ongoing screening studies.

Contributors

The study was undertaken and analysed under the auspices of the steering committee, who are the authors of the paper. J Cuzick and A Szarewski were the project leaders from June, 1998, to the end of the trial. They and P Sasieni were responsible for the original concept. J Cuzick, A Szarewski, P Sasieni, H Kitchener, and D Luesley contributed to the design of the protocol. J Cuzick, P Sasieni, C Brooks, and R Edwards were primarily responsible for statistical analysis and or interpretation of data. All authors were involved in writing the paper, provided important suggestions for revision, and approved the final version submitted for publication. G Hulman, H Kitchener, D Luesley, E McGoogan, U Menon, M Desai, C Gie, I Jacobs, and C Pickles were responsible for recruitment and local implementation and coordination. H Cubie, G Terry, and L Ho did all HPV testing. R Edwards was responsible for local and remote data systems and randomisation.

Pathology review committee

Main reviewer—M Anderson (Queen's Medical Centre, Nottingham [retired]).

Other committee members—C H Buckley (St Mary's Hospital, Manchester) A Williams (University Medical School, Edinburgh).

Study collaborators

Recruitment of patients—J Chapman (St Bartholomew's Hospital, London), C Collins (City Hospital, Birmingham), G Gilkison (University Medical School, Edinburgh), S Goralik (The King's Mill Centre, Mansfield), C Graham (St Mary's Hospital, Manchester), J Hufton (The King's Mill Centre, Mansfield), A Myers (St Mary's Hospital, Manchester), L O'Connor (St Bartholomew's Hospital, London), K Sibley (St Bartholomew's Hospital, London).

HPV testing—P Londesborough (University College, London), C Moore (Specialist Virology Centre, Royal Infirmary of Edinburgh), L Seagar (Specialist Virology Centre, Royal Infirmary of Edinburgh).

Colposcopy—P Bryan (City Hospital, Birmingham), G Beattie (St John's Hospital, Edinburgh), S Maloney (The King's Mill Centre, Mansfield), A Tomlinson (St Mary's Hospital, Manchester).

Conflict of interest statement

The study was partly funded by a grant from Digene Corporation. J Cuzick is a consultant for Digene Corporation. H Cubie and P Sasieni have received travel grants from Digene Corporation. E McGoogan has received support from Cytoc Corporation to attend international scientific meetings.

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