



HPV testing in combination with liquid-based cytology in primary cervical screening (ARTISTIC): a randomised controlled trial

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Summary

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Background Testing for human papillomavirus (HPV) DNA is reportedly more sensitive than cytology for the detection of high-grade cervical intraepithelial neoplasia (CIN). The effectiveness of HPV testing in primary cervical screening was assessed in the ARTISTIC trial, which was done over two screening rounds approximately 3 years apart (2001–03 and 2004–07) by comparing liquid-based cytology (LBC) combined with HPV testing against LBC alone.

Methods Women aged 20–64 years who were undergoing routine screening as part of the English National Health Service Cervical Screening Programme in Greater Manchester were randomly assigned (between July, 2001, and September, 2003) in a ratio of 3:1 to either combined LBC and HPV testing in which the results were revealed and acted on, or to combined LBC and HPV testing where the HPV result was concealed from the patient and investigator. The primary outcome was the detection rate of cervical intraepithelial neoplasia grade 3 or worse (CIN3+) in the second screening round, analysed by intention to treat. This trial is registered with the International Standard Randomised Controlled Trial Number ISRCTN25417821.

Findings There were 24 510 eligible women at entry (18 386 in the revealed group, 6124 in the concealed group). In the first round of screening 233 women (1·27%) in the revealed group had CIN3+, compared with 80 (1·31%) women in the concealed group (odds ratio [OR] 0·97, 95% CI 0·75–1·25; $p>0\cdot2$). There was an unexpectedly large drop in the proportion of women with CIN3+ between the first and second rounds of screening in both groups, at 0·25% (29 of 11 676) in the revealed group and 0·47% (18 of 3866 women) in the concealed group (OR 0·53, 95% CI 0·30–0·96; $p=0\cdot042$). For both rounds combined, the proportion of women with CIN3+ were 1·51% (revealed) and 1·77% (concealed) (OR 0·85, 95% CI 0·67–1·08; $p>0\cdot2$).

Interpretation LBC combined with HPV testing resulted in a significantly lower detection rate of CIN3+ in the second round of screening compared with LBC screening alone, but the effect was small. Over the two screening rounds combined, co-testing did not detect a higher rate of CIN3+ or CIN2+ than LBC alone. Potential changes in screening methodology should be assessed over at least two screening rounds.

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Introduction

In primary cervical screening, human papillomavirus (HPV) testing is more sensitive than cytology for the detection of high-grade cervical intraepithelial neoplasia (CIN), although it has been shown to be less specific, especially in younger women.¹ HPV testing is approved in the USA for primary screening when co-testing with cytology, and is also approved for the triage of women with atypical cells of undetermined significance (ASCUS) cytology, as it has a high negative predictive value and greater sensitivity than repeat cytology.^{2,3} Randomised trials comparing conventional cytology plus HPV testing with cytology alone in Sweden⁴ and the Netherlands⁵ recently reported increased detection of high-grade CIN in the initial (prevalence) round, reduced incidence in the subsequent round, and no difference when the two rounds were combined. Liquid-based cytology (LBC) has replaced conventional Papanicolaou cytology as the platform for cervical

cytology in the UK, and is replacing conventional cytology in a number of other developed countries. Advantages of LBC include more rapid screening of slides, a substantial reduction in unsatisfactory cervical samples requiring repeat testing,⁶ and a cellular residue suitable for HPV testing. ARTISTIC is the first randomised trial to report a comparison of LBC plus HPV testing against LBC testing alone in primary screening. The aim of the study was to determine whether combined testing would result in a reduced incidence of high-grade disease in the second screening round compared with LBC alone.

Methods

Patients

Women aged 20–64 years attending after receiving a routine invitation for screening within the National Health Service Cervical Screening Programme (NHSCSP) were recruited in general practice and family-planning clinics

For the ARTISTIC protocol see <http://www.ncchta.org/projects/1162.asp>

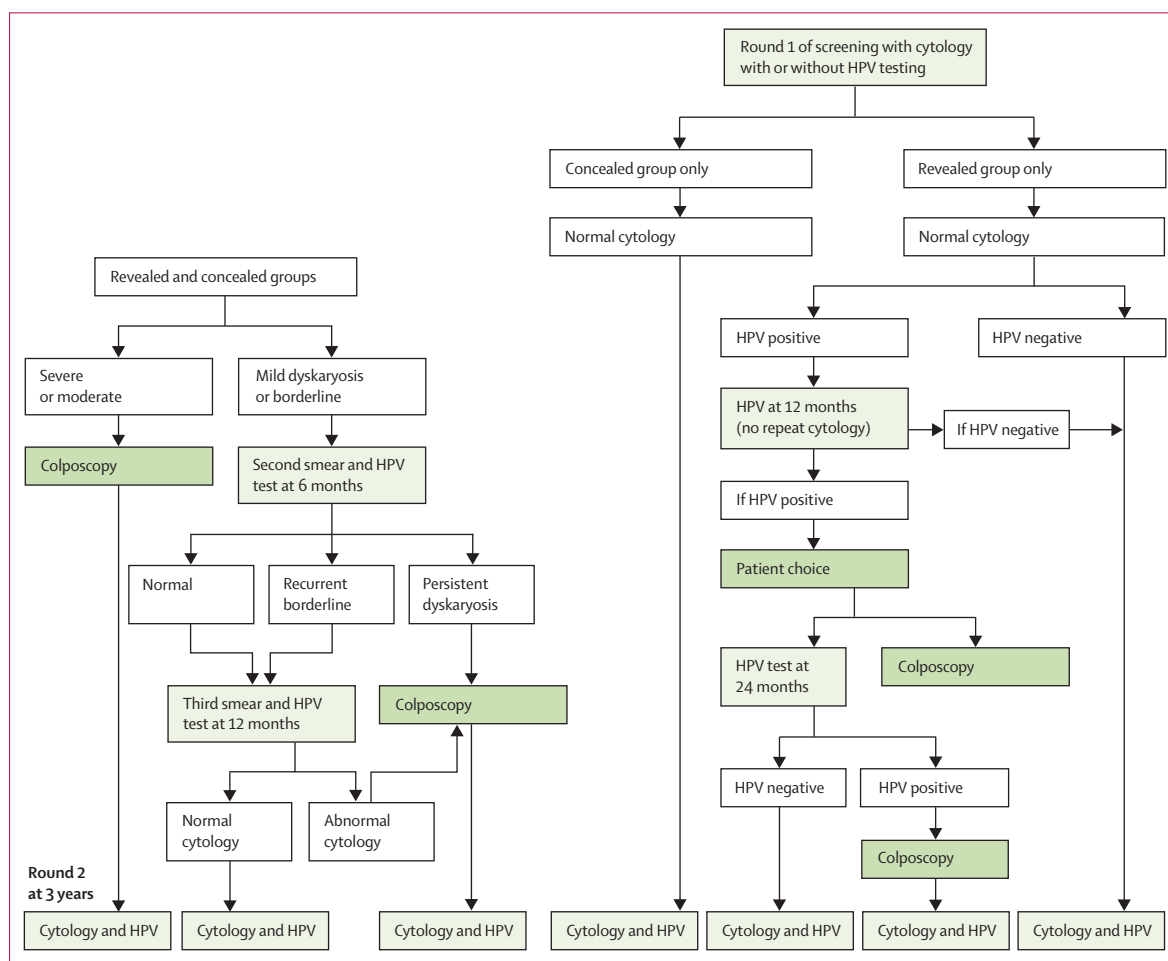


Figure 1: Clinical management and timelines according to cytology grade in screening round 1 and by study group

in Greater Manchester. The study was approved by the North West Multicentre Regional Ethics Committee. An information sheet describing the trial was sent with the invitation for screening, and signed informed consent was obtained. All women had both cytology and HPV testing, and were randomly assigned at a ratio of 3:1 to have the HPV result reported and acted on (revealed group) or concealed from the woman and her doctor (concealed group). Simple randomisation was considered appropriate given the sample size. When the consent form was received, a researcher located in a separate office, and not otherwise involved in the trial, attached an allocation using a list prepared by one of the trial statisticians using computer-generated random numbers.

All women were invited for a second screening (round 2) 36 months after they attended their first screen. HPV-positive women with negative cytology in the revealed group were offered colposcopy at 12 months if they were still HPV positive, and again at 24 months if they chose not to have colposcopy at 12 months.⁷ Trial numbers, 10-digit NHS numbers, and dates of birth were used as personal identifiers and were stored in a Microsoft

Access 2000 database, which also held data on randomisation, cytology, HPV testing, and histology sample numbers with corresponding dates of collection and reporting.

Procedures

Slides were prepared from LBC samples on a ThinPrep T3000 processor (Hologic; Crawley, UK) at the Manchester Cytology Centre. Slides from Stockport residents were returned to Stepping Hill Hospital Cytology Laboratory in Stockport for reading. Liquid residues of LBC samples were tested for HPV at the virology laboratory at Manchester Royal Infirmary. Cytology was reported using the classification of the British Society of Cervical Cytology. With respect to the Bethesda classification, negative equates to within normal limits, borderline to ASCUS, mild dyskaryosis to low-grade squamous intraepithelial lesion (LSIL), and moderate or severe dyskaryosis to high-grade squamous intraepithelial lesion (HSIL).

Testing for high-risk HPV DNA was done according to manufacturer's instructions using the Digene Hybrid

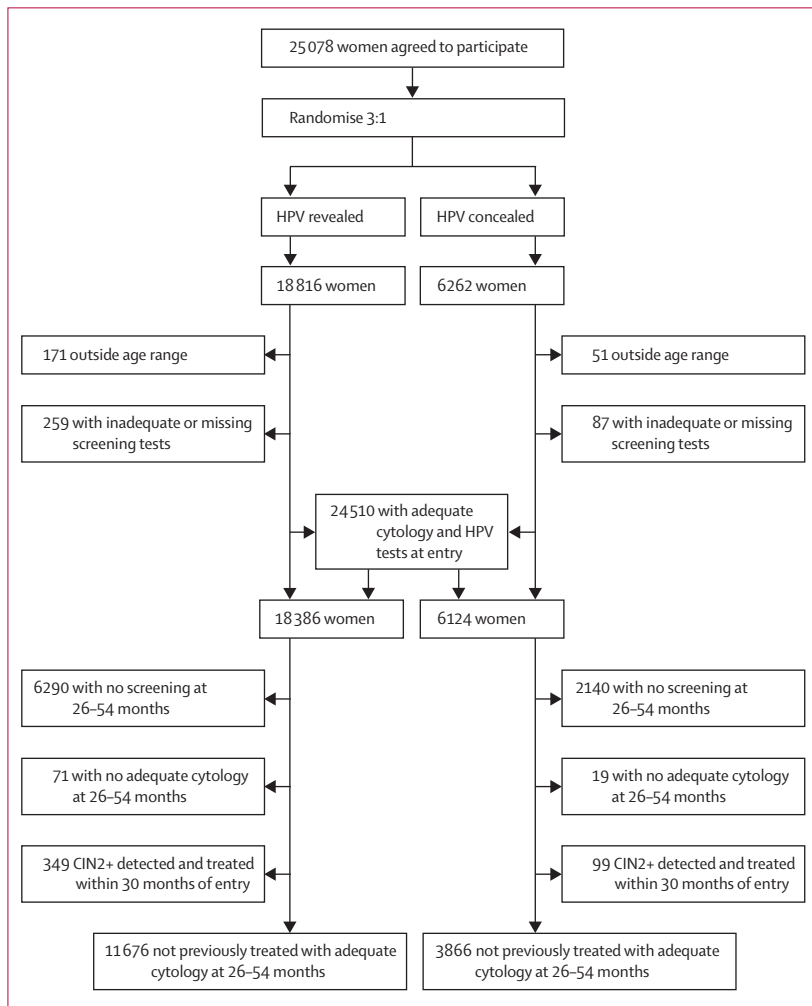


Figure 2: CONSORT diagram of the ARTISTIC trial

Capture 2 (HC2, Qiagen; Crawley, UK) test.⁸ This nucleic acid microplate chemiluminescent detection assay detects 13 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). Results were read and calculated on the Digene Microplate Luminometer 2000 (DML 2000; Qiagen, Crawley, UK) using the HC2 software at the recommended relative light units to control ratio of greater than or equal to 1.0. HPV results were reported independently of both cytology and histopathology.

High-grade CIN histology based on loop excision samples was classified as CIN3 or worse (CIN3+) or CIN2 or worse (CIN2+). A result of CIN1 or less was usually based on a punch biopsy without further excision. Only one biopsy counted per woman. If a punch biopsy and an excisional biopsy were taken, the higher grade of CIN was used.

All colposcopists were accredited by the British Society of Colposcopy and Clinical Pathology, and colposcopy was done according to national guidelines. Colposcopy was done for women with a single high-grade (moderate or

severe) cytological abnormality. Women with a low-grade (borderline or mild) cytological abnormality were referred for colposcopy after two consecutive mild dyskaryosis or three consecutive borderline results. Biopsy samples were taken in the presence of an abnormality; random punch biopsy samples were not taken in cases of negative, satisfactory colposcopy. High-grade cytology required a biopsy, and if not a punch biopsy, a loop excision of the transformation zone was done. The clinical management according to cytology grade and randomised group with timelines is shown in figure 1.

Cytology was reported blinded to the HPV result, and vice versa, for HPV testing. Histopathology was reported blinded to the HPV result. Colposcopists were aware of HPV-positive and cytology-negative reports in the revealed group, but colposcopy was done in a standard manner whether cytology was abnormal or normal.

Women were eligible if they were aged 20–64 years when they provided a round-1 sample that was defined as the first cytologically adequate sample after randomisation at entry that gave a satisfactory HPV result. Many women attended for their next routine screen earlier or later than the scheduled 3-year recall. To minimise exclusions, the round-2 entry sample was therefore defined as the first cytologically adequate sample taken between 26 and 54 months after the date of the round-1 entry sample. Women were classified histologically at round 1 and round 2 on the basis of the highest grade of histology within 30 months of abnormal round-1 or round-2 cytology (both groups), or of a cytologically normal but persistently HPV-positive sample triggering referral for colposcopy within 30 months of a round-1 sample (revealed group only for round 1). CIN2+ histology following a cytologically normal round-2 sample was ignored to make the diagnostic criteria for round-2 results the same in the revealed and concealed groups. All women were followed for cytology and histology until April 30, 2007, and histology records were updated until July 31, 2008, for women who had attended round 2. Histology results after these dates (July 31, 2008, for women who attended round 2, April 30, 2007, for all other women) were ignored.

Statistical analysis

There was a planned age weighting in the protocol to achieve sufficient numbers of HPV infections and CIN2+ lesions in older women. The planned target for women aged under 30 years was reached in November, 2002, and participating clinics were asked to limit subsequent recruitment to women aged 30 years or over. The protocol had specified a planned accrual of 28 000 women, but the cytological abnormality rate and HPV-positive rates were higher than predicted in our pre-trial calculation, so the target power had been reached with 24 000 women. The 3:1 revealed:concealed randomisation ratio was designed to provide adequate

power to detect a reduction in high-grade disease in the revealed group in round 2 while maximising the number of cytology-negative plus HPV-positive women in round 1 who were recalled after 12 months for a second HPV test. Assuming a 1% rate of moderate or severe dyskaryosis, the trial had 90% power to detect a 40% reduction in high-grade dyskaryosis between the concealed and revealed groups in round 2. At the time of the planned analysis, the trial-management group determined that histology should be the primary outcome measure, in common with other recently published trials. CIN3+ is the primary outcome, although CIN2+ is also presented for comparison with studies that report HSIL histology.

CIN3+ and CIN2+ detection rates in round 1, round 2, and overall were compared on an intention-to-treat basis. Women with CIN2+ histology at round 1 have been excluded from the analyses of round-2 results, so detection rates across both rounds can be estimated by combining the observed proportions of CIN2+ and CIN3+ in women screened in round 1 with those in round 2.

All significance tests are two-sided. Fisher's exact test was used for comparing the proportions in each group with high-grade histology in round 1 (p_1) and round 2 (p_2). The proportion for rounds 1 and 2 combined (p) was calculated from $\log(1-p) = \log(1-p_1) + \log(1-p_2)$. The CI for p was calculated for the binomial proportion n/N , choosing the integers n and N giving the best approximations for $p = n/N$ and $\text{var } \log(1-p) = (1-p)/(N \cdot p) = \text{var } \log(1-p_1) + \text{var } \log(1-p_2)$. Between-group comparisons for p were also based on these binomial proportions. Odds ratios (ORs) and their CI were calculated by unconditional logistic regression. All analyses were programmed in STATA version 10.

Role of the funding source

The funding source reviewed and approved the study design, but were not involved in data collection, analysis, interpretation, or in writing the paper. All authors had access to the raw data. The corresponding author had final responsibility to submit the manuscript for publication.

Results

Between July 1, 2001, and Sept 30, 2003, 25 078 women agreed to participate in the trial and were randomised, of whom 222 were outside the age range (20–64 years) and 346 had inadequate screening tests. All analyses are restricted to the remaining 24 510 eligible women, 18 386 of whom were randomly assigned to the revealed group and 6124 of whom were randomly assigned to the concealed group (figure 2). At the time of the analysis 16 080 (65.6%) had attended round-2 cytology 26–54 months after entry to round 1, including 448 with CIN2+ detected and treated in round 1 and 90 whose round 2 cytology was inadequate (table 1). The round-2 analyses shown in table 2, table 3, and table 4 are based

	Revealed group		Concealed group	
	Number in round 2 (% of round 1)	Total in round 1	Number in round 2 (% of round 1)	Total in round 1
Age group (years)				
20–24	1059 (54.8)	1933	343 (53.4)	642
25–29	1094 (56.2)	1946	363 (56.3)	645
30–39	3711 (64.8)	5725	1223 (64.7)	1889
40–49	3265 (71.0)	4601	1055 (69.6)	1516
50–64	2967 (71.0)	4181	1000 (69.8)	1432
Cytology				
Negative	10 391 (64.8)	16 042	3417 (64.0)	5338
Borderline (ASCUS)	965 (71.9)	1343	323 (72.4)	446
Mild (LSIL)	470 (73.1)	643	170 (72.3)	235
Moderate+ (HSIL)	270 (75.4)	358	74 (70.5)	105
HPV testing				
Negative	10 231 (65.9)	15 526	3373 (65.2)	5171
Positive	1865 (65.2)	2860	611 (64.1)	953
Total	12 096 (65.8)	18 386	3984 (65.1)	6124

ASCUS=atypical cells of undetermined significance. HSIL=high-grade squamous intraepithelial lesion. LSIL=low-grade squamous intraepithelial lesion. Round 2 is defined as the first cytologically adequate LBC sample taken 26–54 months after entry to round 1. Includes 90 women whose round-2 sample was cytologically inadequate and 448 who attended for round 2 but had CIN2+ histology diagnosed and treated in round 1.

Table 1: Number and percentage of women screened in round 1 who attended for round 2 of screening, by age, cytology, and HPV status at entry to round 1

on the 11 676 women in the revealed group and 3866 in the concealed group with adequate follow-up cytology and no CIN2+ in round 1. Records were updated until the end of April, 2007, for cytology and until the end of July, 2008, for histology. Therefore follow-up for histology after round-2 screening was at least 30 months for women seen before February 2006 (71% of round-2 cytologies), 24–30 months for women seen between February and July, 2006 (19% of round-2 cytologies), and 15–24 months for the remaining 10%. Based on the interval from cytology to histological diagnosis of the 73 round-2 CIN2+ cases in women with 30 months of histological follow-up (65 less than 18 months, six within 18–24 months, and two within 24–30 months), less than two additional round-2 CIN2+ cases are expected when 30 months of histological follow-up is available for all 15 542 women with round-2 cytology. Follow-up for round-2 histology is therefore virtually complete. The round-2 results are based on CIN3+ and CIN2 cases detected by round-2 screening 26–54 months after entry, but all cases in both rounds, including those excluded in table 4 by our definitions of the round-2 sample, are shown by allocated group in table 2 or listed in its footnote.

In the revealed group 1675 (9.1%) out of 18 386 women tested cytology negative but HPV positive in round 1. Of

	Revealed group				Concealed group			
	HPV negative	HPV positive	No HPV test	Total	HPV negative	HPV positive	No HPV test	Total
Round 1 HPV, cytology, and histology results								
Negative cytology	14367	1675	na	16042	4787	551	na	5338
CIN2	1*	22	na	23	0	0	na	0
CIN3+	0	10	na	10	0	0	na	0
Borderline (ASCUS) cytology	923	420	na	1343	309	137	na	446
CIN2	16	30	na	46	3	14	na	17
CIN3+	2	29	na	31	2	7	na	9
Mild (LSIL) cytology	196	447	na	643	69	166	na	235
CIN2	2	52	na	54	1	16	na	17
CIN3+	1	39	na	40	0	11	na	11
Moderate+ (HSIL) cytology	40	318	na	358	6	99	na	105
CIN2	5	93	na	98	1	18	na	19
CIN3+	4	148	na	152	0	60	na	60
Total in round 1	15526	2860	na	18386	5171	953	na	6124
CIN2	24	197	na	221	5	48	na	53
CIN3+	7	226	na	233	2	78	na	80
Round 2 HPV, cytology, and histology results								
Negative cytology	9334	683	1084	11101	3064	224	368	3656
CIN2	2*	10*	2*	14	0	0	0	0
CIN3+	0*	5*	1*	6	0	1*	0	1
Borderline (ASCUS) cytology	189	105	51	345	69	37	29	135
CIN2	3	5	0	8	1	5	0	6
CIN3+	0	6	2	8	1	4	1	6
Mild (LSIL) cytology	42	107	34	183	6	43	10	59
CIN2	1	11	4	16	0	5	1	6
CIN3+	0	8	0	8	0	3	0	3
Moderate+ (HSIL) cytology	4	37	6	47	1	12	3	16
CIN2	0	10	2	12	0	2	2	4
CIN3+	1	12	0	13	0	8	1	9
Total in round 2	9569	932	1175	11676	3140	316	410	3866
CIN2	6	36	8	50	1	12	3	16
CIN3+	1	31	3	35	1	16	2	19

na=not applicable. *CIN2+ cases that did not follow an HPV positive sample in round 1 (revealed group only) or abnormal cytology (both rounds, both groups) are indicated with an asterisk and excluded in subsequent tables and figures. A further 18 CIN2+ histologies were diagnosed during the trial follow-up. Nine had histology more than 30 months after round 2 (three CIN2 and four CIN3+ in the revealed group, two CIN3+ in the concealed group); eight had no round-2 smear recorded but had histology before May, 2007 (four CIN2 and one CIN3+ in the revealed group, two CIN2 and one CIN3+ in the concealed group); and one CIN2 (revealed group) histology was determined over 30 months after entry but before the round-2 smear.

Table 2: Cytology and histology results in rounds 1 and 2 (highest grade histology within 30 months of either round)

these, 62.1% (1040 of 1675 women) attended for repeat HPV testing before round 2, 42.2% (439 of 1040) of whom were still HPV positive. Of these, 66.3% (291 of 439) underwent colposcopy within 30 months of entry.

Follow-up rates at round 2 of screening by age, cytology, and HPV status at entry are shown in table 1. The overall follow-up rate was higher in older women and in those who were cytologically abnormal at round 1, but there was no significant difference in relation to round-1 HPV status or group. The round-2 attendance rate of women

who were cytology negative and HPV positive at entry was virtually identical in the revealed (988 of 1675 women; 59.0%) and concealed (326 of 551 women; 59.2%) groups (table 4). ORs in a multivariate analysis of the round-2 attendance rate increased with age (OR 1.0 age 20–24 years [reference group]; 1.11 [95% CI 0.99–1.24] at age 25–29 years, 1.65 [1.50–1.81] at age 30–39 years; 2.19 [1.98–2.42] at age 40–49 years; and 2.24 [2.03–2.48] at age 50–64 years; p for trend <0.001) and cytological grade at round 1 (OR 1.0 normal [reference]; 1.55 [95% CI 1.39–1.73] for borderline; 1.86 [1.58–2.18] for mild; and 2.00 [1.60–2.50] for moderate or severe; p for trend <0.001) but were not significant for HPV positivity (OR 0.99, 95% CI 0.91–1.08; p=0.86) or randomisation group (revealed vs concealed OR 1.04, 0.97–1.10; p=0.27). We used a multivariate logistic regression model to compare the characteristics of 6248 women attending for round 2 after 26–35.9 months with 9294 women attending for round 2 36–54 months after round 1. After adjusting for randomisation, age, HPV status, and cytology at entry, there was no difference in time to round 2 between the groups (revealed vs concealed OR 0.96, 95% CI 0.89–1.04; p=0.36). Separate analyses of each group showed that older women and those who tested positive in round 1 for cytology in both groups and for HPV in the revealed group attended earlier, but these analyses suggest that all comparisons between the groups are unbiased.

The cytology and histology results by HPV status for both groups in round 1 and 2 are shown in table 2, with positive-predictive values shown in table 3. The overall rate of borderline or worse cytology was 12.8% (12.2% [2067 of 16 948] in Manchester and 14.1% [1063 of 7562] in Stockport) in round 1. This resulted in colposcopy referral rates of 5.2% (320 of 6124) and 6.8% (1247 of 18 386) in the concealed and revealed groups, respectively. The higher rate in the revealed group was due to colposcopy for cytologically normal women who remained HPV positive on retesting. The borderline or worse cytology rate decreased to 5.1% (5.2% [578 of 11 188] in Manchester and 4.8% [207 of 4354] in Stockport) in round 2. This large reduction in cytological abnormality rates from round 1 to round 2 was seen in both groups (table 2). The rate of moderate dyskaryosis or worse decreased five-fold, from 1.9% (463 of 24 510) in round 1 to 0.4% (63 of 15 542) in round 2, and borderline or mild dyskaryosis decreased from 10.9% (2667 of 24 510) in round 1 to 4.6% (722 of 15 542) in round 2. Part of this difference reflected an initial increase and subsequent decrease in the reported abnormality rate after the introduction of LBC when the trial began in July, 2001. The cytological abnormality rate (borderline or worse) was 16.8% in the first 6 months of recruitment, and the age-adjusted OR in round 1 for any abnormality in successive 6-month periods decreased from 1.0 (reference: July to December, 2001) to 0.75 (95% CI 0.68–0.82), 0.71 (0.64–0.79), 0.60 (0.53–0.69), and

0.61 (0.49–0.76). We therefore compared round-1 cytology results in women randomised in 2003 (the last year of recruitment) whose preceding smear record on the cytology laboratory's database was cytologically normal and taken 26–54 months earlier, against round-2 results for women in the concealed group whose round-1 smear was normal. Age when the relevant round-1 or round-2 smear was taken was included in the model (30–39 years, 40–49 years, and 50 years and over; women aged under 30 years were no longer being recruited in 2003). The age-adjusted round 2 *vs* round 1 OR was 0.44 (95% CI 0.20–0.98) for moderate or worse dyskaryosis and 0.47 (0.37–0.61) for borderline or worse, indicating a marked reduction in all grades of cytology independent of the initial LBC learning curve.

Table 4 shows the primary outcome of the trial, the overall difference in CIN3+ rates in round 2 by allocated group. Analyses for all women and for those who were cytologically normal and HPV positive at enrolment are shown. Overall CIN3+ rates in round 1 were 1.27% (233 of 18386) in the revealed group, including ten CIN3+ cases in cytologically normal women, and 1.31% (80 of 6124) in the concealed group (OR 0.97, 95% CI 0.75–1.27; *p*>0.2). The round-2 results in table 4 exclude

90 women whose round-2 cytology was inadequate, and 448 women with high-grade histology treated in round 1 (see figure 3).

The reduction in high-grade cytology was reflected in much lower proportions with CIN3+ and CIN2 in round 2, with 586 of 24510 (2.4%) CIN2+ cases in round 1 and only 99 of 15542 (0.6%) in round 2. The proportion of women with CIN3+ in round 2 was 0.25% (29 of 11676) in the revealed group and 0.47% (18 of 3866) in the concealed group (OR 0.53, 95% CI 0.30–0.96; *p*=0.042). The proportion of women with CIN2+ in round 2 was 0.56% (65 of 11676) in the revealed group and 0.88% (34 of 3866) in the concealed group (OR 0.63, 95% CI 0.41–0.99; *p*=0.035). When rounds 1 and 2 were combined, the overall detection rates in the two groups of the trial were similar for both CIN3+ (1.51% revealed, 1.77% concealed [OR 0.85, 95% CI 0.67–1.08; *p*>0.2]) and CIN2+ (3.01% revealed, 3.03% concealed [OR 0.99, 0.83–1.19; *p*>0.2]). For women who were cytologically negative and HPV positive at entry, the proportions with CIN3+ in round 2 were 1.52% (15 of 988, revealed) *vs* 2.15% (seven of 326, concealed), but this difference was not statistically significant.

	Revealed group				Concealed group			
	HPV negative	HPV positive	No HPV test	Total	HPV negative	HPV positive	No HPV test	Total
Round 1 HPV, cytology and histology results for CIN2+								
Negative*	na	1.9 (1.3–2.7)	na	na	na	na	na	na
Borderline (ASCUS)	2.0 (1.2–3.1)	14.0 (10.9–17.7)	na	5.7 (4.6–7.1)	1.6 (0.5–3.7)	15.3 (9.7–22.5)	na	5.8 (3.8–8.4)
Mild (LSIL)	1.5 (0.3–4.4)	20.4 (16.7–24.4)	na	14.6 (12.0–17.6)	1.4 (0.04–7.8)	16.3 (11.0–22.8)	na	11.9 (8.1–16.8)
Moderate+ (HSIL)	22.5 (10.8–38.5)	75.8 (70.7–80.4)	na	69.8 (64.8–74.5)	16.7 (0.4–64.1)	78.8 (69.4–86.4)	na	75.2 (65.9–83.1)
Overall rate in round 1	0.2 (0.1–0.3)	14.8 (13.5–16.1)	na	2.5 (2.2–2.7)	0.1 (0.05–0.3)	13.2 (11.1–15.5)	na	2.2 (1.8–2.6)
Round 2 HPV, cytology and histology results for CIN2+								
Negative*	na	na	na	na	na	na	na	na
Borderline (ASCUS)	1.6 (0.3–4.6)	10.5 (5.3–18.0)	3.9 (0.5–13.5)	4.6 (2.7–7.4)	2.9 (0.4–10.1)	24.3 (11.8–41.2)	3.4 (0.09–17.8)	8.9 (4.7–15.0)
Mild (LSIL)	2.4 (0.06–12.6)	17.8 (11.0–26.3)	11.8 (3.3–27.5)	13.1 (8.6–18.9)	0.0	18.6 (8.4–33.4)	10.0 (0.3–44.5)	15.3 (7.2–27.0)
Moderate+ (HSIL)	25.0 (0.6–80.6)	59.5 (42.1–75.2)	33.3 (4.3–77.7)	53.2 (38.1–67.9)	0.0	83.3 (51.6–97.9)	100.0	81.3 (54.4–96.0)
Overall rate in round 2	0.05 (0.02–0.1)	5.6 (4.2–7.3)	0.7 (0.3–1.3)	0.6 (0.4–0.7)	0.06 (0.008–0.2)	8.5 (5.7–12.2)	1.2 (0.4–2.8)	0.9 (0.6–1.2)
Round 1 HPV, cytology and histology results (CIN3+ rate [%])								
Negative*	na	0.6 (0.3–1.1)	na	na	na	na	na	na
Borderline (ASCUS)	0.2 (0.03–0.8)	6.9 (4.7–9.8)	na	2.3 (1.6–3.3)	0.6 (0.08–2.3)	5.1 (2.1–10.2)	na	2.0 (0.9–3.8)
Mild (LSIL)	0.5 (0.01–2.8)	8.7 (6.3–11.7)	na	6.2 (4.5–8.4)	0.0	6.6 (3.4–11.5)	na	4.7 (2.4–8.2)
Moderate+ (HSIL)	10.0 (2.8–23.7)	46.5 (41.0–52.2)	na	42.5 (37.3–47.8)	0.0	60.6 (50.3–70.3)	na	57.1 (47.1–66.8)
Overall rate in round 1	0.05 (0.02–0.09)	7.9 (6.9–9.0)	na	1.3 (1.1–1.4)	0.04 (0.005–0.1)	8.2 (6.5–10.1)	na	1.3 (1.0–1.6)
Round 2 HPV, cytology and histology results (CIN3+ rate [%])								
Negative*	na	na	na	na	na	na	na	na
Borderline (ASCUS)	0.0	5.7 (2.1–12.0)	3.9 (0.5–13.5)	2.3 (1.0–4.5)	1.4 (0.04–7.8)	10.8 (3.0–25.4)	3.4 (0.09–17.8)	4.4 (1.6–9.4)
Mild (LSIL)	0.0	7.5 (3.3–14.2)	0.0	4.4 (1.9–8.4)	0.0	7.0 (1.5–19.1)	0.0	5.1 (1.0–14.4)
Moderate+ (HSIL)	25.0 (0.6–80.6)	32.4 (18.0–49.8)	0.0	27.7 (15.6–42.6)	0.0	66.7 (34.9–90.1)	33.3 (0.8–90.6)	56.3 (29.9–80.2)
Overall rate in round 2	0.01 (0.0003–0.06)	2.8 (1.8–4.1)	0.2 (0.02–0.6)	0.2 (0.2–0.4)	0.03 (0.0008–0.2)	4.7 (2.7–7.7)	0.5 (0.06–1.8)	0.5 (0.3–0.7)

na=not applicable. *HPV-positive CIN2+ cases with negative cytology in the revealed group are included in round 1 results. All other CIN2+ cases following negative cytology are excluded (shown with asterisk in table 2).

Table 3: Positive predictive values (PPVs) and 95% CIs for CIN2+ and CIN3+ in screening rounds 1 and 2 by randomisation group, HPV status, and cytology

	HPV revealed		HPV concealed		Revealed vs concealed	
	N	Prevalence (95% CI)	N	Prevalence (95% CI)	OR (95% CI)	p
Round 1: all women						
Number of women randomised	18 386		6124			
CIN2	220	1.20% (1.04-1.36)	53	0.87% (0.65-1.13)	1.39 (1.03-1.88)	0.035
CIN3+	233	1.27% (1.11-1.44)	80	1.31% (1.04-1.62)	0.97 (0.75-1.25)	>0.2
CIN2+	453	2.46% (2.24-2.70)	133	2.17% (1.82-2.57)	1.14 (0.94-1.38)	>0.2
Round 2: all women						
Number of women	11 676		3866			
CIN2	36	0.31% (0.22-0.43)	16	0.41% (0.24-0.67)	0.74 (0.41-1.34)	>0.2
CIN3+	29	0.25% (0.17-0.36)	18	0.47% (0.28-0.73)	0.53 (0.30-0.96)	0.042
CIN2+	65	0.56% (0.43-0.71)	34	0.88% (0.61-1.23)	0.63 (0.42-0.96)	0.035
Round 1 plus round 2: all women						
CIN2	256	1.50% (1.32-1.70)	69	1.28% (0.99-1.62)	1.18 (0.90-1.55)	>0.2
CIN3+	262	1.51% (1.33-1.71)	98	1.77% (1.43-2.16)	0.85 (0.67-1.08)	>0.2
CIN2+	518	3.01% (2.75-3.28)	167	3.03% (2.59-3.53)	0.99 (0.83-1.19)	>0.2
Round 1: women with negative cytology and HPV positive test at entry to round 1						
Number of women	1675		551			
CIN2	22	1.31% (0.82-1.98)	0	na	na	na
CIN3+	10	0.60% (0.29-1.10)	0	na	na	na
CIN2+	32	1.91% (1.31-2.69)	0	na	na	na
Round 2: women with negative cytology and HPV positive test at entry to round 1						
Number of women	988		326			
CIN2	13	1.32% (0.70-2.24)	7	2.15% (0.87-4.37)	0.61 (0.24-1.54)	>0.2
CIN3+	15	1.52% (0.85-2.49)	7	2.15% (0.87-4.37)	0.70 (0.28-1.74)	>0.2
CIN2+	28	2.83% (1.89-4.07)	14	4.29% (2.37-7.10)	0.65 (0.34-1.25)	>0.2
Round 1 plus round 2: women with negative cytology and HPV positive test at entry to round 1						
CIN2	35	2.61% (1.81-3.65)	7	2.15% (0.87-4.37)	1.22 (0.54-2.79)	>0.2
CIN3+	25	2.11% (1.35-3.12)	7	2.15% (0.87-4.37)	0.98 (0.42-2.30)	>0.2
CIN2+	60	4.69% (3.56-6.05)	14	4.29% (2.37-7.10)	1.10 (0.60-2.00)	>0.2

na=not applicable. Round 2 was defined as the first adequate cytology taken 26–54 months after entry. Abnormal round 2 cytology on date of histology was assumed for two CIN3 cases diagnosed 29 and 35 months after entry. Three CIN3 cases at round 2 with CIN2 in round 1 were excluded. One CIN2 case (revealed group) was excluded from round 1 due to negative cytology. 14 CIN2, 4 CIN3, and two cancers (revealed group) and a further CIN3 from the concealed group were excluded from round 2 due to negative cytology in round 2 (see table 2).

Table 4: High-grade disease in screening rounds 1, 2, and overall, by randomisation group

A post-hoc sub-group analysis for women aged over 30 years did not result in any additional significant findings, although the CIN3+ rates in the two groups in round 2 no longer showed a significant difference (14 of 9721, 0.14% [revealed] vs nine of 3220, 0.28% [concealed]; $p=0.14$).

The numbers of CIN3+ and CIN2 lesions detected in the revealed group are shown in figure 3 for both screening rounds according to HPV status at entry. Women who were HPV positive at entry (2860 of 18 386 [15.6%] women in the revealed group) accounted for 226 of 233 (97.0%) of CIN3+ cases and 423 of 453 (93.4%) of CIN2+ cases diagnosed in round 1. Only 4.3% (ten of 233) of CIN3+ diagnoses in round 1 were HPV positive and cytologically negative, and 3.0% (seven of 233) were cytologically abnormal and HPV negative.

From the revealed group, we have analysed different combinations of cytology and HPV testing in primary screening and triage with respect to their sensitivities and specificities (relative to the combined testing of the revealed group). Table 5 shows these results both overall and in women aged 20–29, 30–39, and 40–64 years.

Discussion

When primary cervical screening with LBC was combined with HPV testing there was a small but statistically significant reduction in the detection of CIN2+ and CIN3+ at the next screening round compared with LBC alone. When rounds 1 and 2 were combined, LBC with HPV testing did not identify significantly more CIN2+ or CIN3+ cases than LBC alone.

Two outcomes of this large randomised trial were unexpected. First, the number of additional cases of CIN3+ detected in round 1 by adding HPV testing to cytology in the revealed group was small (ten cases) and similar to the number that were cytologically abnormal but HPV negative (seven cases). Other studies reported larger increases in CIN3+ detection as a result of referring cytology-negative but HPV-positive women for colposcopic investigation and lower sensitivity for cytology than for HPV testing.¹ Second, there was a marked reduction from round 1 to round 2 in the prevalence of abnormal cytology, particularly high-grade, which persisted following adjustment for any learning curve of LBC involving high rates of abnormality early in round 1. This large reduction in abnormal cytology in part reflects the much lower prevalence of high-grade histology seen at round 2 (table 4). Table 2 shows that the prevalence of CIN2+ in women with abnormal cytology (PPV) was similar in round 1 (16.9%; 133 of 786) and round 2 (16.2%; 34 of 210) in the concealed group, but in the revealed group the PPV decreased from 18.0% (421 of 2344) in round 1 to 11.3% (65 of 575) in round 2 ($p<0.001$). This is due in part to the reduced prevalence in high-grade disease in round 2 associated with a reduction in abnormal cytology. That the PPV of cytology falls for both CIN2+ and CIN3+ in the revealed group in round 2 has implications for HPV-based primary cervical screening. It could be expected, if cytology were used to triage the management of HPV-positive women, that its performance in terms of PPV would be reduced. The broad definition of 26–54 months was necessary for round 2 to minimise excluded cases of CIN2+, because women respond to recall in an irregular schedule. The similar rates of follow-up and round 1 characteristics between the groups (table 2) suggest that this will not have led to any bias.

Two factors might have contributed to the much lower cytological abnormality rates seen in round 2 than in round 1. First, some prevalent disease detected in round 1 had presumably been missed at the previous routine smear, as LBC in this study might have been more sensitive than earlier cytology in this routinely screened population, due both to the technical advantages of LBC

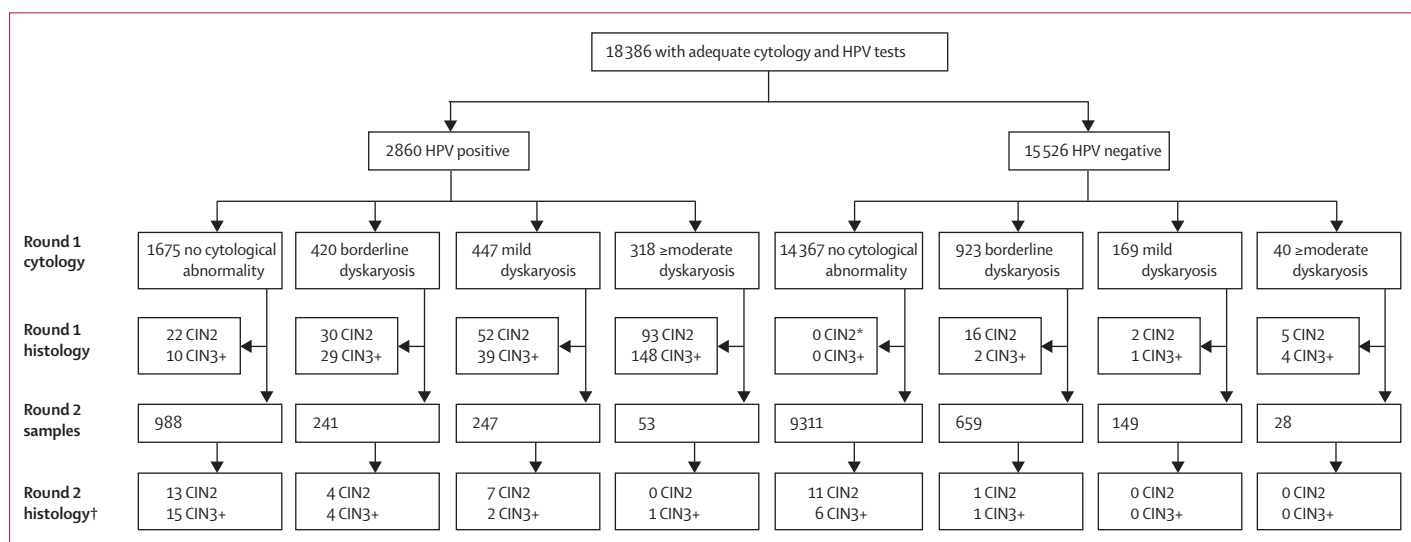


Figure 3: Number of CIN2 and CIN3 or worse (CIN3+) histological lesions detected by cytology in rounds 1 and 2 of screening, and by HPV status in round 1 of screening in the revealed group
 *One case of CIN2 in an HPV-negative and cytology-negative woman was excluded. †Round 1 test results for 20 CIN2+ cases that are excluded in round 2 (starred in table 2): three CIN2, four CIN3+ HPV-positive and cytology-negative; one CIN2, one CIN3+ HPV-positive and cytology borderline; two CIN2 HPV-positive and cytology mild; six CIN2, one CIN3+ HPV-negative and cytology-negative; two CIN2 HPV-negative and cytology-borderline.

over conventional cytology and to the additional training of staff in the community in taking cervical samples, as well as cytology laboratory staff in reading LBC when it was introduced in this region in 2001. The additional sensitivity achieved by LBC or HPV testing must, however, depend on the protocol for colposcopic follow-up, and also on the sensitivity of the conventional cytology against which they are compared, which has varied widely between different regions and over time. The sensitivity of conventional cytology for detecting high-grade CIN varied between 30% and 80% in different European centres in the 1990s.¹ The effectiveness of cervical cytology⁹ despite this limited sensitivity has presumably been the result of repeated rounds of screening. A systematic review¹⁰ of both screening and referral studies, reported mainly between 2001 and 2007, found no difference in sensitivity to detect high-grade CIN between LBC and conventional cytology, but other recent studies have come to a variety of conclusions. A Dutch randomised study¹¹ reported no difference in test positives, but without histological outcomes. Another Dutch study¹² comparing non-randomised groups from a similar geographic area reported increased sensitivity for LBC over conventional cytology for CIN1+ (96.2% vs 92%). In a split-sample study from Australia,¹³ LBC combined with automation resulted in over 20% more CIN2+ lesions detected compared with conventional cytology, with 170 additional biopsies to detect the 71 additional CIN2+ cases. LBC and automated slide presentation of fields at higher risk of abnormality might result in a more consistent range of sensitivity between laboratories.

A second factor may have been additional detection of CIN2 or lesser pathology by LBC, the treatment of which

might prevent some CIN3 lesions in the next screening round. In a randomised trial in Italy, 66% more cytological abnormalities were detected by LBC than by conventional cytology, which led to increased detection of CIN2 although not CIN3+.¹⁴ Comparisons of sensitivity and specificity for the detection of high-grade disease over a single screening round¹ might therefore be misleading, particularly if LBC leads to increased detection and biopsy or treatment of low-grade disease, which prevents progression.

The CIN3+ rates in rounds 1 and 2 of this trial are compared with recently published data from the Swedish SWEDESCREEN⁴ and Dutch POBASCAM⁵ trials in table 6 (the round-2 rates are lower than those shown in table 4, because all randomised women are included in the denominator in table 6). In all three trials, HPV testing in the first screening round detected cases of CIN3+ that were missed by cytology, but there were fewer cases in the combined HPV testing plus cytology group at round 2, and over both screening rounds there were no significant differences (table 6). The higher rate of CIN3+ detected at entry in ARTISTIC might be due partly to differences in HPV prevalence, prior levels of screening, and the age ranges of these populations. The high rate of low-grade cytological abnormality in round 1 resulted in an overall colposcopy rate of 5.2% in the concealed group and 6.8% in the revealed group, and this probably increased the detection rate of CIN. Data from the National Cervical Screening Programme indicate that the national colposcopy referral rate following routine cytology is around 3%.¹⁵

A striking difference between these trials is the much smaller increase in CIN3+ detection at entry in ARTISTIC

	CIN2+		n (%) referred for colposcopy	CIN2+ specificity (% [95% CI])	CIN3+	
	n (%) CIN2+ not detected	CIN2+ sensitivity (% [95% CI])			n (%) CIN3+ not detected	CIN3+ sensitivity (% [95% CI])
Women aged 20–29 years (n=3879; 236 CIN2+, 117 CIN3+)						
Cytology alone	20 (8.5)	91.5 (87.2–94.7)	874 (22.5)	81.9 (80.6–83.2)	5 (4.3)	95.7 (90.3–98.6)
Cytology with HPV triage of borderline lesions	27 (11.4)	88.6 (83.8–92.3)	696 (17.9)	86.6 (85.5–87.7)	6 (5.1)	94.9 (89.2–98.1)
HPV with cytology triage	31 (13.1)	86.9 (81.9–90.9)	645 (16.6)	87.9 (86.8–89.0)	8 (6.8)	93.2 (87.0–97.0)
HPV with cytology triage and repeat HPV if cytology negative	11 (4.7)	95.3 (91.8–97.7)	1325 (34.2)	69.8 (68.3–71.2)	3 (2.6)	97.4 (92.7–99.5)
Cytology and HPV testing and repeat HPV if cytology negative	0	100	1554 (40.1)	63.8 (62.2–65.4)	0	100
Women aged 30–39 years (n=5725; 152 CIN2+, 82 CIN3+)						
Cytology alone	9 (5.9)	94.1 (89.1–97.3)	754 (13.2)	89.0 (88.2–89.8)	4 (4.9)	95.1 (88.0–98.7)
Cytology with HPV triage of borderline lesions	15 (9.9)	90.1 (84.2–94.4)	442 (7.7)	94.5 (93.9–95.1)	4 (4.9)	95.1 (88.0–98.7)
HPV with cytology triage	21 (13.8)	86.2 (79.7–91.2)	365 (6.4)	95.8 (95.2–96.3)	7 (8.5)	91.5 (83.2–96.5)
HPV with cytology triage and repeat HPV if cytology negative	12 (7.9)	92.1 (86.6–95.9)	872 (15.2)	86.9 (86.0–87.7)	3 (3.7)	96.3 (89.7–99.2)
Cytology and HPV testing and repeat HPV if cytology negative	0	100	1261 (22.0)	80.1 (79.0–81.1)	0	100
Women aged 40–64 years (n=8782; 65 CIN2+, 34 CIN3+)						
Cytology alone	3 (4.6)	95.4 (87.1–99.0)	716 (8.2)	92.5 (91.9–93.0)	1 (2.9)	97.1 (84.7–99.9)
Cytology with HPV triage of borderline lesions	8 (12.3)	87.7 (77.2–94.5)	283 (3.2)	97.4 (97.1–97.7)	2 (5.9)	94.1 (80.3–99.3)
HPV with cytology triage	10 (15.4)	84.6 (73.5–92.4)	175 (2.0)	98.6 (98.4–98.9)	2 (5.9)	94.1 (80.3–99.3)
HPV with cytology triage and repeat HPV if cytology negative	7 (10.8)	89.2 (79.1–95.6)	663 (7.5)	93.1 (92.5–93.6)	1 (2.9)	97.1 (84.7–99.9)
Cytology and HPV testing and repeat HPV if cytology negative	0	100	1204 (13.7)	86.9 (86.2–87.6)	0	100
All women (n=18 386; 453 CIN2+, 233 CIN3+)						
Cytology alone	32 (7.1)	92.9 (90.2–95.1)	2344 (12.7)	89.3 (88.8–89.7)	10 (4.3)	95.7 (93.2–97.9)
Cytology with HPV triage of borderline lesions	50 (11.0)	89.0 (85.7–91.7)	1421 (7.7)	94.3 (94.0–94.7)	12 (5.2)	94.8 (91.2–97.3)
HPV with cytology triage	62 (13.7)	86.3 (82.8–89.3)	1185 (6.4)	95.6 (95.3–95.9)	17 (7.3)	92.7 (88.6–95.7)
HPV with cytology triage and repeat HPV if cytology negative	30 (6.6)	93.4 (90.7–95.5)	2860 (15.6)	86.4 (85.9–86.9)	7 (3.0)	97.0 (93.9–98.8)
Cytology and HPV testing and repeat HPV if cytology negative	0	100	4019 (21.9)	80.1 (79.5–80.7)	0	100

Table 5: Relative sensitivity and specificity for CIN2+ and sensitivity for CIN3+ under different screening policies based on 220 CIN2 and 233 CIN3+ histologies detected in 18 386 women in the revealed group in round 1

	Number of women randomised		CIN3+ in round 1				CIN3+ in round 2			CIN3+ over both rounds	
	Cytology only	HPV tested	Cytology only (n [per 1000])	HPV tested (abnormal entry cytology)	HPV tested (normal entry cytology)	Total (n [per 1000])	Cytology only (n [per 1000])	HPV tested (n [per 1000])	Cytology only (n [per 1000])	HPV tested (n [per 1000])	
POBASCAM	8580	8575	40 (4.7)	55	13	88 (7.9)	54 (6.3)	24 (2.8)	94 (11.0)	92 (10.7)	
SWEDESCREEN	6270	6257	55 (8.8)	56	16	72 (11.5)	30 (4.8)	16 (2.6)	85 (13.6)	88 (14.1)	
ARTISTIC	6124	18 386	80 (13.1)	223	10	233 (12.7)	18 (2.9)	29 (1.6)	98 (16.0)	262 (14.2)	

Results for round 2 and for both rounds combined are based on all randomised women irrespective of follow-up. Age-range at entry was 29–56 years for POBASCAM; 32–38 years for SWEDESCREEN, and 20–64 years for ARTISTIC. The round-1 to round-2 interval was 5 years in POBASCAM, and 3 years in both SWEDESCREEN and ARTISTIC. Follow-up for round-1 histology was 48 months for POBASCAM, 19 months for SWEDESCREEN, and 30 months for ARTISTIC. Round-2 screening in POBASCAM was by conventional cytology plus HPV, conventional cytology in SWEDESCREEN, and LBC in ARTISTIC.

Table 6: Proportion of women with CIN3+ detected over two rounds of screening in randomised screening trials of cytology with and without HPV testing

through HPV testing among cytologically normal women, with only 4.5% (ten of 223) additional CIN3+ cases diagnosed compared with 24% (13 of 55) in POBASCAM and 29% (16 of 56) in SWEDESCREEN.¹⁶ There are three factors that might explain this difference.

First, the introduction of LBC led to a marked initial increase in abnormal cytology, and hence referral for colposcopy, which increased sensitivity and reduced specificity. This led to enhanced detection and treatment of underlying lesions. Second, some cytology-negative

and HPV-positive women were still HPV positive on retesting, but did not attend colposcopy within 30 months of entry. The round-1 and round-2 comparisons between groups are dependent on the conventions used to define rounds, and the combined round-1 plus round-2 comparison is probably more meaningful in such studies. The third factor is that the referral and colposcopy policies for cytology-negative and HPV-positive women differed in the randomised trials, with repeat HPV test and cytology at 12 months with colposcopy and biopsy for all referred cases (SWEDESCREEN and POBASCAM), and repeat HPV test at 12 or 24 months with directed biopsy for referred cases (ARTISTIC). The different reported sensitivities of HPV testing over a single screening round presumably reflect these differences in cytology, referral, and colposcopy protocols.

There are also differences in detection rates between rounds 1 and 2 in the cytology-only group, where the CIN3+ rate decreased more than four-fold (13·1 of 1000 vs 2·9 of 1000) in ARTISTIC, less than two-fold in SWEDESCREEN (8·8 of 1000 vs 4·8 of 1000), and increased slightly in POBASCAM (4·7 of 1000 vs 6·3 of 1000). A contributing factor may be the longer scheduled follow-up between rounds in POBASCAM (5 years) than in ARTISTIC and SWEDESCREEN (3 years). The follow-up for round 1 histology also varied (18 months in SWEDESCREEN, 30 months in ARTISTIC, and 48 months in POBASCAM). A pooled analysis of these apparently disparate results with uniform definitions of round-1 and round-2 histology rates would require individual data on all cytology and subsequent histology, as well as age and HPV status.

There are unavoidable statistical deficiencies in such data, despite strict randomisation, but these are unlikely to have affected our principal conclusions: that the increased sensitivity achieved with HPV testing was small at entry and negligible over two screening rounds, and that cytological and histological abnormality prevalence rates were greatly reduced in round 2. This large study was conducted in the real-life setting of routine screening within the National Cervical Screening Programme, and the 66% compliance with re-screening within the timeframe and catchment area of the study reflects the routine data available in this context, but there is no evidence that this biased our results.

Over two rounds this trial showed no evidence that LBC combined with HPV testing in primary cervical screening detected more CIN2 or CIN3+ than cytology alone. This summed effect over two rounds is relevant because screening relies on repeated rounds to achieve its sensitivity. This finding was confirmed by the two other recently reported randomised trials,^{4,5} but greater sensitivity than reported here was achieved by HPV testing compared with cytology in the prevalence (first) round of both the Swedish and Dutch trials. The unexpectedly low prevalence of cytological abnormality in round 2 of ARTISTIC has other important implications

for future developments in cervical screening. The relative sensitivities and specificities of different screening policies in round 1 of ARTISTIC are shown in table 5. Repeat HPV testing in cytologically normal women achieved slightly improved sensitivity for CIN2+, but specificity was reduced in women aged under 30 years. However, the results on the revealed group in round 2 show a different pattern, with much lower abnormality rates but a higher proportion of high-grade histology presenting with HPV infection but normal cytology.

ARTISTIC will continue through to a third round of screening 6 years after enrolment, which will determine whether HPV testing could extend screening intervals because of the longer duration of protection conferred by a negative HPV result than by a negative LBC finding. HPV testing as a single initial screen would require a follow-up protocol conferring greater specificity, at least in younger women, and possibly a modified colposcopy protocol for cytologically normal women with persistent HPV, which could include random biopsy when colposcopy is negative.¹⁷ Reassuringly, published psychosocial data from ARTISTIC indicated that the addition of HPV testing to cytology did not cause psychological distress.¹⁸ The HC2 test does not distinguish between the different high-risk HPV types, but typing positive women will become important if HPV testing is introduced as a primary screening test, both to identify type-specific persistence on retesting and to monitor the long-term effect of HPV16 and HPV18 vaccination.

Contributors

HCK, JP, SM, RD, BS, MD, and CR all contributed to study design. HCK, JP, and RD contributed to drafting. JP, MA, CG, HB, and CR contributed to the statistical analysis. AS, AB, and AT did the virological analyses. MD and JM supervised and coordinated the cytological activity. PW and CT acted as trial co-ordinators. All authors contributed to revision of the manuscript.

Conflicts of interest

MD has undertaken unpaid consultancy for Hologic. All other authors declared no conflicts of interest.

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