Human papillomavirus testing with conventional Pap smear screening in three inner London community clinics

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Abstract

Background and methodology This observational study aimed to establish prevalence of high-risk human papillomaviruses (hrHPV) in women attending three inner London community clinics for routine screening and to pilot hrHPV testing in the triage of either borderline or negative cytology after previous abnormalities. Hybrid Capture® 2 was carried out on brush samples taken alongside conventional smears from 1434 women aged 20–49 years. hrHPV positivity prompted earlier referral of women with previous abnormalities and either low-grade or negative cytology. Outcome at colposcopy was compared with the records of 1871 women aged 20–49 years attending colposcopy during the same period of time (routine colposcopies).

Results hrHPV was detected in 111/161 (68.9%) women with abnormal cytology, 76/460 (16.5%) with negative cytology after previous abnormalities and 105/813 (12.9%) with negative cytology and no previous abnormalities. Overall, hrHPV was detected in 292/1434 (20.4%) women in the study (95% CI 18.3–22.5). hrHPV prevalence increased with severity of cytological abnormality ($p<0.001$) and decreased with age both with negative and low-grade cytology ($p<0.001$). High-grade cervical intraepithelial neoplasia (CIN) biopsies were found more frequently in women in the study groups with low-grade ($p<0.001$) or negative cytology than in routine colposcopies, but more women in the study groups attended colposcopy (8.2% compared with 4.1% routine colposcopies, $p<0.001$).

Conclusions hrHPV positivity increased detection of high-grade CIN in the study groups at the expense of more colposcopies. hrHPV negativity could reduce the need for investigation of low-grade cytology in women aged over 35 years and for surveillance after previous abnormalities.

Keywords cervical intraepithelial neoplasia, colposcopy, cytological surveillance, human papillomavirus testing, low-grade cytology triage

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Introduction

High-risk types of human papillomavirus (hrHPV) are recognised as the primary cause of cervical cancer[1] and the sensitivity of testing for hrHPV with Hybrid Capture® 2 (HC2) has been shown to be greater than cytology alone for detecting high-grade cervical intraepithelial neoplasia (CIN).[2]

HC2 was the first commercially available method of testing for hrHPV.[3] It was used in the National Health Service Cervical Screening Programmes (NHSCSP) study of triage of women with borderline cytology together with liquid-based cytology (LBC) at two of the three LBC pilot sites.[4] HC2 is also being used in the ARTISTIC trial in the UK, the cross-sectional results of which have recently been published.[5] HC2 was also used in the ALTS trials in the USA, where it is now recommended as an option for triage of women with atypical squamous cells of undetermined significance[6,7] and has been used effectively for that purpose.[8,9]

The aims of this study were three-fold:

- To establish the prevalence of hrHPV in women undergoing routine cervical screening in an inner London population.
- To assess the value of hrHPV testing alongside conventional cytology in the management of women with borderline cytology.
- To assess the role of hrHPV testing in women with negative cytology and a past history of cervical abnormalities.

The present study differs from HPV testing carried out in NHSCSP LBC pilot site studies in several respects, namely the use of brush samples rather than residual material in LBC vials, the use of anonymous hrHPV testing

Key message points

- **This observational study demonstrated high-risk human papillomavirus (hrHPV) prevalence of 20.4% in a population of routinely screened women aged 20–49 years. Prevalence decreased with age and decreasing degree of cytological abnormality.**
- **hrHPV testing was used to triage women with borderline and negative cytology after previous abnormalities and increased detection of high-grade cervical intraepithelial neoplasia at the expense of more colposcopies.**
- **The results suggested that negative hrHPV testing could reduce the need for investigation of women aged over 35 years with low-grade cytology and for surveillance after previous abnormalities.**

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in women with consistently negative cytology, and the use of hrHPV testing to manage women with negative follow-up cytology whether or not they had received treatment.

Apart from the potential for hrHPV testing to improve detection of high-grade CIN and cervical glandular intraepithelial neoplasia (CGIN), negative results in women with low-grade cytology or a history of previous abnormalities might avert the need for colposcopy or even frequent cytological surveillance. In England as a whole, the NHSCSP achievable range for low-grade cytology (mild dyskaryosis and borderline combined) was 4.0–9.1% of tests during the period of the study.[10] With three annual follow-up smears recommended after any low-grade abnormality and ten annual follow-ups after treatment of high-grade CIN[11] there is a large number of women on annual follow-up for previous abnormalities.

The cytological diagnosis of borderline nuclear change (BNC) is subjective, and in many instances reflects non-specific inflammatory and other changes unrelated to cervical cancer or pre-cancer. The National Institute for Clinical Excellence (NICE) identified triage of cytological borderline changes and follow-up after treatment of CIN as potential roles for hrHPV testing[12] but there has been no previous assessment of its use in follow-up of low-grade abnormalities that appear on cytology to have regressed. The sensitivity and negative predictive value (NPV) of HC2 have been shown to approach 100% when combined with negative cytology,[13] which might allow less frequent surveillance of women with previous abnormalities.

Methods

Study population and specimens

A total of 1434 women aged 20–49 years were recruited for the study between January 2002 and October 2003. These women were attending three community reproductive health clinics in the London Borough of Lambeth for routine cervical screening. Women gave written consent for HPV testing of their cell sample if the cytology was abnormal or if they gave a past history of cytological abnormality: in either instance the HPV result would be used alongside the cytology to decide optimal management. Otherwise, they gave consent for the HPV test result to be anonymous. The number of women who refused consent for the trial was minimal and is unlikely to have affected the results.

A conventional smear was prepared with an Aylesbury spatula after which a cell sample was taken for HC2 testing for hrHPV using a Digene cervical brush sampler rinsed into liquid transport medium (Digene Corporation, Gaithersburg, MD). This was the protocol used for the HART study[15] and was recommended by Digene.

Study Groups A, B and C

Group A: abnormal cytology

Group A comprised 161 women with a cytology result of dyskaryosis or borderline (Table 1). Cytological assessment was recorded before the HC2 result was available; the final report recorded both results and gave a recommendation for management.

hrHPV detection was used as a surrogate for mild dyskaryosis for which, in the local programme, the test is repeated on its second occurrence. Thus, hrHPV positivity in mild dyskaryosis or BNC was an indication for referral only if there had been a previous abnormality and had little effect on referral of women with mild dyskaryosis. Women with BNC were referred on second rather than third occurrence if hrHPV was detected. Women with moderate, ungraded or severe dyskaryosis were referred irrespective of the hrHPV result.

Group B: negative smears after previous abnormalities

Group B comprised 460 women with negative or inadequate follow-up smears after previous abnormalities, with or without treatment (Table 1). The largest category in this group comprised 267 women on follow-up for low-grade cytology or CIN1 biopsies within the preceding 5 years. Fifty-seven women had low-grade cytology or biopsy recorded more than 5 years before, 50 had high-grade cytology or biopsy within 5 years, and 22 more than 5 years before. In 64 instances, details of the previous abnormality could not be ascertained beyond the information provided by the patient that a previous smear had been abnormal. Details of previous treatment were not always available but it may be assumed that those with previous high-grade cytology would have been treated. Some of those on follow-up for low-grade cytology would have been treated but most would have been managed by cytological surveillance with or without colposcopy.

Detection of hrHPV in women with negative cytology was an indication for referral if there was a past history of abnormal cytology or treatment of CIN using the same criteria as would be used for mild dyskaryosis. Repeat cytology was usually recommended when the previous low-grade cytology was more than 5 years previously.

Group C: negative smears and no previous abnormality

Group C comprised 813 women with negative or inadequate cytology and no history of abnormal cytology. Once the cytology result was known to be either negative or inadequate the HC2 tests in Group C were anonymised and not linked to the woman's cervical cytology record at any stage. There are therefore no follow-up data for this group.

Comparison with routine colposcopies

Outcome at colposcopy in Study Groups A and B was compared with the laboratory records of 1871 women aged 20–49 years referred for colposcopy during the same period of time (routine colposcopies) but excluding those in the study. These data were taken from spreadsheets held for audit and quality control purposes.

Hybrid Capture 2

Samples were analysed by HC2 according to the manufacturer's instructions (Digene Corporation) using the B-cocktail probe which targets DNA from 13 hrHPV types. [NB. HC2 utilises specific RNA probes, hybridisation, antibody capture and signal amplification to allow rapid, standardised detection of HPV DNA.] Results were calculated using Digene's software programme, which provides results as RLU/CO (Relative Light Units/Cut-Off). RLU/CO results >1.0 were taken as positive. Positive and negative hrHPV calibrators and internal quality control samples were included in each test run.

Statistical analysis

Pearson's Chi-square tests were used to assess associations between categorical variables, except where Fisher's exact test was used when more than 20% of the cells in cross-tabulation had an expected count of 5. The change in hrHPV detection rate by ordered categories was assessed by a non-parametric test for trend against ordered groups.[14]

Ethical approval

Ethical approval for the study was obtained from the local ethics committee.

Table 1 High-risk human papillomavirus (hrHPV) results according to cytology result, previous history and age group

Study group	Age group in years [hrHPV detected/total tested = *n/n* (%)]											
	Total		20–24		25–29		30–34		35–39		40–44		45–49	
Group A: abnormal cytology (*n* = 161)	111/161	(68.9)	37/44	(84.1)	39/52	(75.0)	15/19	(78.9)	15/26	(57.7)	4/16	(25.0)	1/4	(25.0)
Borderline (n = 75)	43/75	(57.3)	16/21	(76.2)	12/19	(63.2)	6/9	(66.7)	7/12	(58.3)	2/11	(18.2)	0/3	(0.0)
Mild (n = 61)	46/61	(75.4)	16/18	(88.9)	15/19	(78.9)	6/6	(100.0)	6/12	(50.0)	2/5	(40.0)	1/1	(100.0)
Moderate (n = 17)	14/17	(82.4)	5/5	(100.0)	7/9	(77.8)	1/2	(50.0)	1/1	(100.0)	0/0	(0.0)	0/0	(0.0)
Severe (n = 8)	8/8	(100.0)	0/0	(0.0)	5/5	(100.0)	2/2	(100.0)	1/1	(100.0)	0/0	(0.0)	0/0	(0.0)
Group B: negative cytology, previous abnormality (*n* = 460)	76/460	(16.5)	14/39	(35.9)	20/110	(18.2)	17/122	(13.9)	11/92	(8.1)	6/54	(11.1)	8/43	(18.6)
Low-grade <5 years (*n* = 267)	52/267	(19.5)	10/27	(37.0)	13/68	(19.1)	9/67	(13.4)	8/49	(16.3)	6/32	(18.8)	6/24	(25.0)
Low-grade >5 years (*n* = 57)	9/57	(15.8)	1/1	(100.0)	3/10	(30.0)	2/16	(12.5)	1/13	(7.7)	0/8	(0.0)	2/9	(22.2)
High-grade <5 years (*n* = 50)	5/50	(10.0)	2/5	(40.0)	1/19	(5.3)	1/13	(7.7)	1/12	(8.3)	0/1	(0.0)	0/0	(0.0)
High-grade >5 years (*n* = 22)	3/22	(13.6)	0/0	(0.0)	0/1	(0.0)	2/5	(40.0)	1/8	(12.5)	0/4	(0.0)	0/4	(0.0)
Abnormality unknown (*n* = 64)	7/64	(10.9)	1/6	(16.7)	3/12	(25.0)	3/21	(14.3)	0/10	(0.0)	0/9	(0.0)	0/6	(0.0)
Group C: negative cytology, no previous abnormality (*n* = 813)	105/813	(12.9)	34/138	(24.6)	37/242	(15.3)	17/172	(9.9)	7/113	(6.2)	5/93	(5.4)	5/55	(9.1)
Totals: Groups A, B and C (*n* = 1434)	292/1434	(20.4)	85/221	(38.5)	96/404	(23.8)	49/313	(15.7)	33/231	(14.3)	15/163	(9.2)	14/102	(13.7)

Results

Conventional cytology results in the total population

Of the total 1434 cytology tests, 75 (5.2%) were inadequate. Among the 1359 adequate smears, the cytology reporting rates were as follows: 0.6% severe dyskaryosis (including one ?glandular neoplasia), 1.8% moderate dyskaryosis (including five 'dyskaryosis, grade uncertain'), 4.4% mild dyskaryosis and 5.5% borderline.

hrHPV results by age, cytological abnormality and history

Total study population (Groups A, B and C)

The overall hrHPV prevalence was 20.4% (292/1434, 95% CI 18.3–22.5) ranging between 38.5% (aged 20–24 years) and 9.2% (aged 40–44 years) with a slight increase (13.7%) in women aged 45–49 years compared with age 40–49 years (Table 1). Prevalence declined significantly with age ($p<0.001$). Of 292 women with hrHPV detected in Groups A, B and C combined, cytology was negative in 181 (62.0%), low-grade (mild or borderline) in 89 (30.5%) and high-grade (moderate or severe dyskaryosis) in 22 (7.5%) (Table 1). The percentage with abnormal cytology declined significantly with age ($p<0.001$). The distribution of hrHPV-positive cases according to age and cytology is shown in Figure 1.

There was no significant difference between hrHPV detection in those with negative (170/1198, 14.2%, 95% CI 12.3–16.3) and inadequate smears (11/75, 14.7%, 95% CI 7.6–24.7) in Groups B and C combined. Inadequate smears have therefore been included with negative smears for all

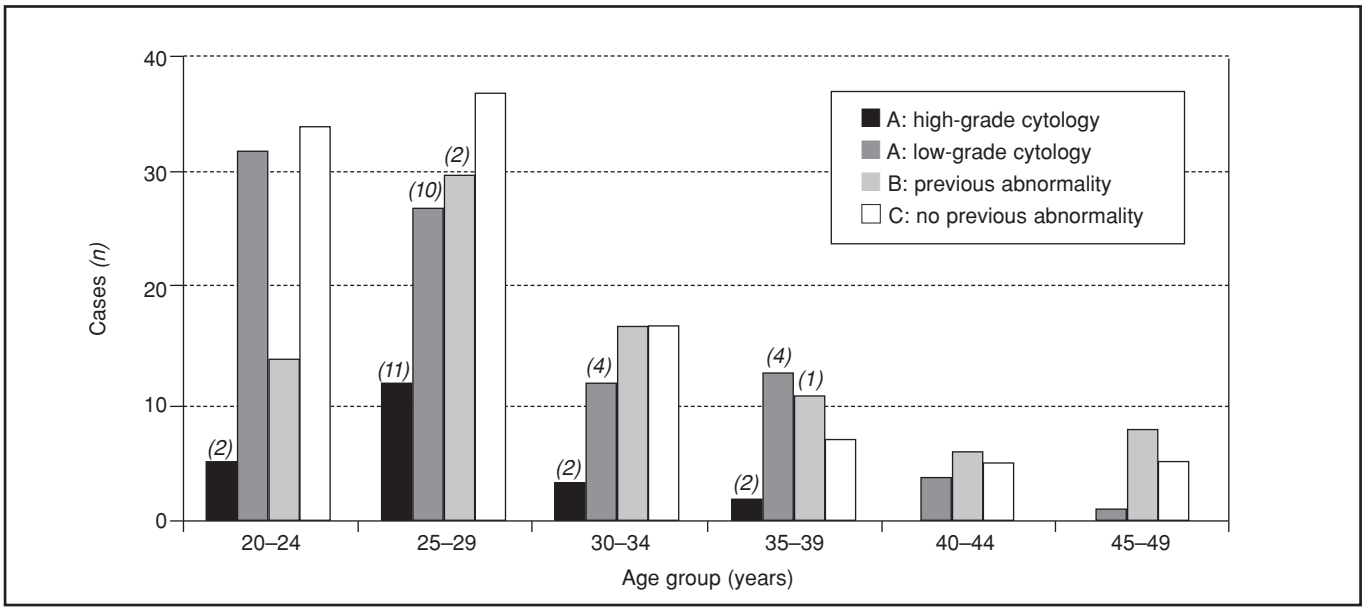

Figure 1 Cytology of 292 high-risk human papillomavirus (hrHPV)-positive women and distribution of high-grade cervical intraepithelial neoplasia (CIN) biopsies according to age for study Groups A, B and C. (*n*) = distribution of 38 high-grade CIN biopsies

Table 2 Outcome in women in the study attending colposcopy compared with routine colposcopies

Study group	Total colposcopy [*n* (%)]	Biopsy results at colposcopy (*n*)					PPV (%)	
		CIN3+	CIN2	CIN1	Koilocytosis/ no CIN	No CIN (or negative colposcopy)	CIN2+	CIN1+
Cytology: Group A and B	118[15] (100.0)	15	24[1]	19[2]	15[3]	45[9]	33.1	49.2
Moderate or worse	25[3] (21.2)	11	6	1	2[1]	5[2]	68.0	72.0
Mild	35[4] (29.7)	1	7	8	10[2]	9[2]	22.9	45.7
Borderline	27[4] (22.9)	2	8	5[2]	2	10[2]	37.0	55.6
Negative/inadequate	31[4] (26.3)	1	3[1]	5	1	21[3]	12.9	29.0
Cytology: Group A and B, hrHPV detected	103	15	23	17	12	36	36.9	53.4
Cytology: routine colposcopies	1871 (100.0)	313	277	467	333	481	31.5	56.5
Moderate or worse	753 (40.2)	268	184	157	64	80	60.0	80.9
Mild	696 (37.2)	28	69	238	171	190	13.9	48.1
Borderline	353 (18.9)	17	24	66	86	160	11.6	30.3
Negative/inadequate	69 (3.7)	0	0	6	12	51	0.0	8.7

[n]Number of hrHPV not detected. CIN, cervical intraepithelial neoplasia; hrHPV, high-risk human papillomavirus; PPV, positive predictive value.

the analyses. We believed this to be justified because in our experience a single inadequate smear is rarely abnormal on repeat and the numbers (75 in all groups combined) were therefore considered to be too small to conceal significant numbers of abnormalities.

Group A: abnormal cytology

The hrHPV-positive rate increased with severity of the cytological abnormality (p = 0.012): 57.3% (43/75) in borderline, 75.4% (46/61) in mild, 82.4% (14/17) in moderate and 100% (8/8) in severe dysksaryosis (Table 1). The three cases with moderate dyskaryosis that were negative for hrHPV were among five reported as 'dyskaryosis, grade uncertain' but managed as moderate.

hrHPV prevalence decreased with age in women with low-grade cytology (p<0.001) but not with high-grade cytology (p = 0.05). No high-grade dyskaryosis was reported in women aged 40–49 years (Figures 1 and 2).

Group B: negative smears after previous abnormalities

hrHPV was detected in 76 (16.5%) of 460 women with negative cytology after previous abnormalities. In this group, 52/267 (19.5%) had low-grade abnormalities within 5 years, 9/57 (15.8%) had low-grade abnormalities more than 5 years before, 5/50 (10%) had high-grade abnormalities within 5 years, 3/22 (13.6%) had high-grade abnormalities more than 5 years before and 7/64 (10.9%) had previous abnormalities that could not be verified (Table 1). There were no significant differences in prevalence of hrHPV between any of these groups but prevalence differed significantly by age group (p for trend = 0.015).

Group C: negative smears and no previous abnormality

hrHPV was detected in 105/813 (12.9%) women with negative smears and no previous abnormality. The prevalence was slightly lower than Group B (16.5%) but not statistically significant (p = 0.077). There was an association with age as in Group B (p<0.001).

Outcome for women in Groups A and B attending colposcopy

Colposcopy results

Colposcopy results in the study were compared with those

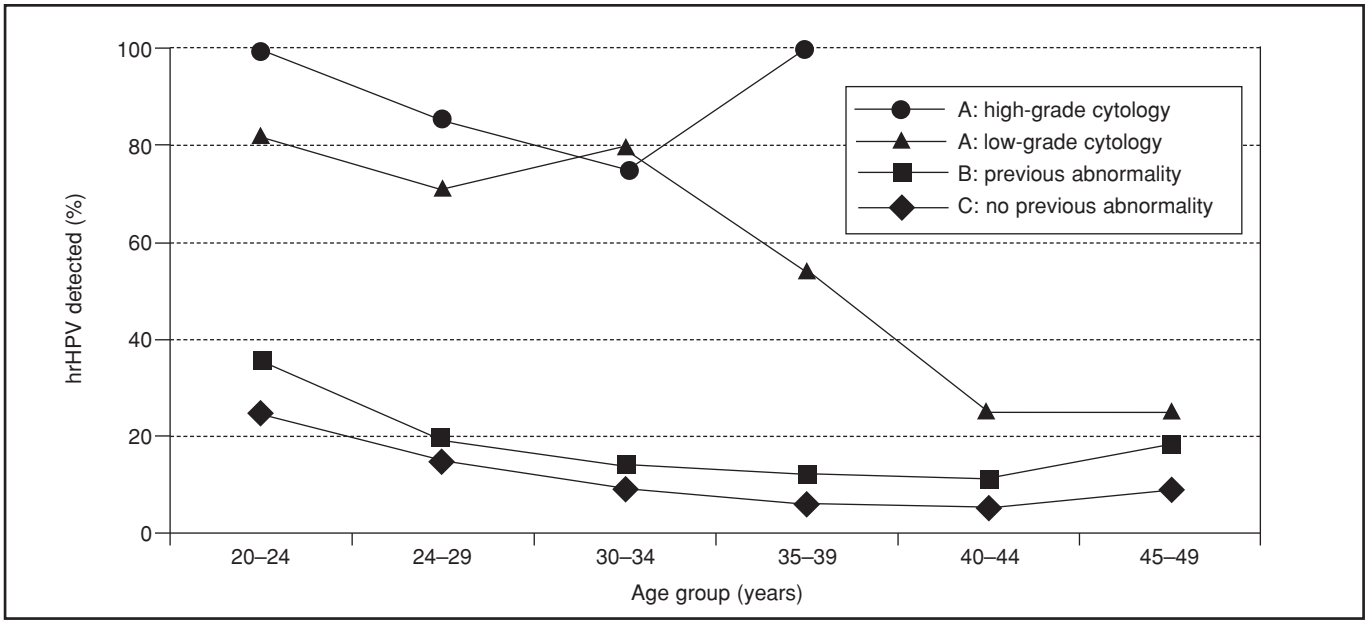

Figure 2 High-risk human papillomavirus (hrHPV) prevalence according to age and cytology result for Study Groups A, B and C

of 1871 routine colposcopies, which comprised 4.1% of 45 159 women aged 20–49 years routinely screened during the same period of time (calculated from laboratory records and Korner returns). Colposcopy was carried out in 118/1434 (8.2%) women in the study, which was a significantly higher percentage compared with routine screening ($p<0.001$). The outcome of colposcopies in the study groups is compared with routine colposcopies in Table 2.

hrHPV was detected in 103/118 (87.3%) women attending colposcopy (Table 2). The positive predictive value (PPV) for histologically confirmed high-grade CIN among 103 hrHPV positive cases in the study population (i.e. excluding those having colposcopy that were hrHPV-negative) was 36.9% (38/103), which was not significantly higher than in the total study population (33.1%, 39/118) or routine colposcopies (31.5%, 590/1871) ($p = 1.0$). Similarly, there was no significant difference in PPV for CIN of any degree among those groups (53.4%; 49.2% and 56.5%; $p = 1.0$). Thus there was no increase in the study groups in the proportion with negative (or koilocytosis only) colposcopy results (Table 2). Of 60 women with negative (or koilocytosis only) results, 12 (20%) were hrHPV-negative.

hrHPV positivity prompted referral for colposcopy in 16/27 (59.3%) women in the study referred for borderline cytology and all of 27 with negative cytology. High-grade CIN was found in 10/27 (37.0%) women referred for borderline cytology compared with 41/353 (11.6%) routine colposcopies ($p<0.001$). High-grade CIN was found in 3/27 (11.1%) women referred for negative smears and hrHPV detected compared with none in routine colposcopies: all three women were on follow-up for low-grade abnormalities within 5 years. High-grade CIN was found in significantly more women in the study referred for mild dyskaryosis and borderline combined (low-grade cytology) compared with routine colposcopies ($p<0.001$) but not for mild dyskaryosis alone ($p = 0.2$). The age distribution of 38 high-grade CIN biopsies among 292 women with hrHPV detected according to cytology result is shown in Figure 1. There was no increase in CIN3+ detection among women in the study compared with routine colposcopies and no invasive cancers were found in the study groups.

Colposcopy was carried out on four women in Group B with negative smears and hrHPV not detected, three of whom had negative colposcopy. One was referred for a subsequent borderline smear and was found to have CIN2. In this case, HPV16 DNA was detected by polymerase chain reaction (PCR) in residual material from the sample taken alongside the original negative cytology test. This woman was the only one aged 45–49 years with high-grade CIN in the study.

Cytological follow-up in Groups A and B

Of 76 women in Group B with hrHPV detected and negative smears, 49 did not have colposcopy and were followed-up cytologically: 31/49 (63.3%) had at least one subsequent negative smear. This was similar to women with borderline cytology in Group A of whom 49 were followed up cytologically and 36 (75.0%) had subsequent negative smears. Of 61 in Group A with mild dyskaryosis, 26 were followed cytologically and 13 (50.0%) had subsequent negative smears. Two in each of those groups had low-grade cytology (without colposcopy) and the remainder were late for repeat cytology or lost to follow-up. Among 384 women with negative hrHPV and negative cytology in Group B follow-up was known for 170 and 166 (97.6%) had at least one subsequent negative smear. Four had subsequent borderline smears of whom one had CIN2 at colposcopy. The remainder were overdue for repeat cytology, lost to follow-up or were not yet due for 3-year recall.

Discussion

Anonymous testing of women with negative cytology and no previous abnormalities allowed information about hrHPV status in the local population to be ascertained while assessing the use of hrHPV testing in the management of women with abnormal current and previous cytology. In the total population 20.4% of women were hrHPV-positive, but the rate declined with age until age 45–49 years when a small increase was observed. There are relatively few studies of hrHPV detection in routine screening populations in England but our results are similar to the cross-sectional results of the ARTISTIC trial.[5] A small increase in prevalence in older women has been reported by others.[15,16] Further testing by PCR and genotyping of HPVs is in progress, as well as further work on the significance of low-level HC2 results (1.0–10.0 RLUs), as recent papers have suggested a higher HC2 cut-off can be used to improve specificity.[17,18]

hrHPV detection rates increased with the degree of cytological abnormality, which was similar to results in the ALTS trial[6,7] and HART study.[15] Our study assessed the value of hrHPV testing for triage of women with persistent low-grade cytology (mild dyskaryosis and borderline) and negative cytology after previous abnormalities. In the former group we demonstrated a striking decline in the hrHPV detection rate with increasing age, which is consistent with other studies.[5,15] hrHPV was detected in between 71.1% and 82.1% of women aged 20–34 years, but in only 25% of women aged 40–49 years. No high-grade CIN was found in women aged 40–49 years except in one woman with CIN2 following a subsequent borderline smear whose test sample was negative for hrHPV by HC2. In England as a whole, more than 80% of CIN3 is diagnosed in women aged less than 40 years.[19] hrHPV testing could reduce the need for colposcopic investigation in women aged over 35 years although the NPV is not 100% as has also been shown in the ARTISTIC trial.[5]

hrHPV detection predicted high-grade CIN in five cases reported as 'dyskaryosis, grade uncertain': CIN3 was found in both cases with hrHPV detected and colposcopy was negative in all three without. These might otherwise have been classified as borderline, high-grade not excluded, as recommended in the proposed British Society for Clinical Cytology (BSCC) terminology,[20] which equates to ASC-H in the 2001 Bethesda System.[21] In the present study, hrHPV positivity was used as a surrogate for mild dyskaryosis in women with borderline and negative follow-up smears, prompting earlier referral to colposcopy. High-grade CIN was found in significantly more women with borderline smears (37% in the study group compared with 11.6% in routine colposcopies; $p<0.001$) and three additional cases of high-grade CIN were found in women with negative smears and hrHPV detected after low-grade cytology within 5 years. The results in our study have been calculated for high-grade CIN comprising CIN2, CIN3 and CGIN (there were no cases of invasive cancer). There was no increased detection of CIN3 in the study, which was similar to the ALTS trial leading to the impression that earlier biopsy may detect cases of CIN2 that would regress if left untreated.[6,7] To achieve this increase in detection of high-grade CIN, twice as many women attended colposcopy compared with routine referrals in the same age group (8.2% compared with 4.1%; $p<0.001$), which is similar to the finding in the NHSCSP pilot site study.[4]

Because of its size and duration, this study provided

limited information about NPV, and one woman who was negative for hrHPV by HC2 had CIN2 after a subsequent borderline smear and was found to be HPV16-positive by PCR in the original sample. No CIN was found in 12/15 (80%) hrHPV-negative women attending colposcopy with smears reported as negative, borderline, mild dyskaryosis or dyskaryosis, grade uncertain: two had CIN1. At least one subsequent negative smear was reported in 165/170 (97.6%) women with negative smears and hrHPV not detected. Negative hrHPV results could reduce the need for investigation of low-grade cytology, particularly in older women (40–49 years) in whom high-grade CIN is rarely found. It would also be informative when combined with cytology review – especially in cases regarded as probably reactive or of unknown significance.

hrHPV testing would have a useful role in follow-up after low-grade cytology as well as after treatment of CIN. Most women could safely return earlier to routine screening while the small percentage with high-grade CIN could be identified among those with hrHPV detected. Currently, three negative annual smears are recommended after low-grade cytology and ten after treatment of high-grade CIN.[11] The percentage in which no hrHPV was detected was not significantly different from the control population, suggesting that cytological surveillance of these women is a safe procedure. No high-grade CIN was found in women with previous high-grade cytological abnormalities, most of whom would have received treatment. The largest follow-up group comprised women with low-grade cytology within 5 years and it was in that group that three cases of high-grade CIN were found.

A small number of high-grade lesions are likely to be harboured in the population with entirely negative screening histories, raising the question of whether hrHPV testing should be used for primary screening. hrHPV was detected in 20.4% of women aged 20–49 years and 17.1% in women aged 25–49 years (as for current NHSCSP screening recommendations). Thus, if used as a primary screening test, more than 80% of women would be hrHPV-negative and would not require cytological screening, which could be concentrated on women at genuine risk for developing pre-cancerous lesions. However, the majority of hrHPV-positive women have negative smears (62% in the present study). The outcome in this potentially large group of women would be comparable to that of women with borderline cytology. As well as requiring regular surveillance until they were hrHPV-negative, these women would need careful counselling to explain the significance of their hrHPV-positive tests. If persistent hrHPV detection was investigated when cytology was negative, occasional cases of cancer that develop in women with negative cytology could be avoided. Furthermore, if rates of abnormality decline when vaccines against common hrHPV types are introduced,[22] there would be an even greater need for a primary screening test that was more sensitive and less labour intensive than cytological screening. Sensitivity of screening is known to be related to the number of abnormalities believed to be present[23] and high-quality cytological screening services would be increasingly difficult to maintain as the prevalence of pre-cancerous lesions declined. Nevertheless, cytology might have a role in triage of hrHPV-positive women.

In summary, although hrHPV testing increased detection of high-grade CIN, its most obvious benefit lay in potentially reducing the need for cytological surveillance in the vast majority of women with negative smears who had no hrHPV detected. Investigation of women aged over 35 years with low-grade cytology could be avoided when hrHPV results were negative.

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Competing interests None identified.

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