CANCER EPIDEMIOLOGY

Attendance at early recall and colposcopy in routine cervical screening with human papillomavirus testing

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Abstract

Attendance at early recall and colposcopy is crucial to attaining the benefits of primary high-risk human papillomavirus (HR-HPV)-based screening. Within the English HPV pilot, we analysed deprivation- and age-related patterns of attendance at colposcopy and 12- and 24-month early recall of HR-HPV positive women screened in 2013 to 2015 (N = 36 466). We fitted logistic regression models for adjusted odds ratios (OR). Despite high overall attendance, area deprivation had a small but significant impact at both early recalls, for example, attendance at 24 months was 86.3% and 83.0% in less vs more deprived areas, respectively (ORadj: 0.76; 95% CI: 0.67-0.87). Older women (≥30 years) were more likely to attend early recall than younger women (<30 years), for example, attendance at 24 months was 86.1% vs 82.3%, respectively (ORadj: 1.32, 95% CI: 1.16-1.51). Most women attended colposcopy following a baseline referral, with 96.9% attendance among more deprived and 97.8% among less deprived areas (ORadj: 0.70; 95% CI: 0.55-0.88). Differences in colposcopy attendance by deprivation level at 12 and 24 months were of approximately the same magnitude. In conclusion, attendance at early recall and colposcopy was reassuringly high. Although there were statistically significant differences by deprivation and age group, these were small in absolute terms.

KEYWORDS

attendance, cervical cancer screening, colposcopy, early recall, human papillomavirus

INTRODUCTION

Not all screen-detected cervical abnormalities need to be investigated with a colposcopy, as some regress spontaneously. Traditionally, cytology-based cervical screening relied on watchful waiting in case of lower-grade abnormalities. Typically, this took the form of repeated testing in early recalls after several months to determine persistence of the abnormality. Early recall was abandoned in the United Kingdom some years ago after the introduction of high-risk human papillomavirus (HR-HPV) triage.1 HR-HPV triage enabled a safe discharge of HR-HPV negative women with low-grade cytological abnormalities to routine recall. By replacing cytology as the primary screening test with HR-HPV testing, however, early recall will be re-introduced for HR-HPV-positive women with negative triage cytology.2 These women harbour an increased risk of underlying high-grade cervical intraepithelial neoplasia (CIN2+).

Abbreviations: ASCUS, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; CSP, Cervical Screening Programme; GP, general practitioner/p Practice; HR-HPV, high-risk human papillomavirus; IMD, index of multiple deprivation; IQR, interquartile range; LBC, liquid-based cytology; NHS, National Health Service.

Henry Kitchener and Matejka Rebolj contributed equally to this work.

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Attendance at the recommended follow-up of HR-HPV infections, be it through a colposcopy or repeat testing at early recall, is crucial to optimise the effectiveness of primary HPV-based screening.\textsuperscript{3} Implementation could, however, be challenging. Although attendance at colposcopy for women referred following abnormal screening tended to be high, the experience from previous research studies suggests that attendance at early recall could be as low as 50% to 60%.\textsuperscript{4,5}

We used the data from the English HPV primary screening pilot to study women’s attendance after colposcopy referral and at early recall in the context of a routine screening programme. We also explored whether incomplete attendance was associated with area-level socioeconomic deprivation and age.

2 | MATERIALS AND METHODS

2.1 | The pilot

In the United Kingdom, the National Health Service (NHS) implemented a cytology-based Cervical Screening Programme (CSP) in 1988. Women aged 25 to 49 years are invited every 3 years, while those aged 50 to 64 years are invited every 5 years. Screening samples are typically taken in primary care.

A pilot within the English CSP, launched in 2013, has confirmed the practicability and safety of HR-HPV testing in a routine setting. This pilot has been described in detail previously.\textsuperscript{6} Briefly, six NHS England screening laboratories converted about a third of their cervical screening operations from liquid-based cytology (LBC) to HR-HPV testing. Tests were allocated by administrative areas to ensure the laboratories were able to consistently deliver the different forms of testing. HR-HPV negative women were recommended for age-appropriate routine recall. HR-HPV positive women were recommended for a colposcopy if they had positive triage cytology at baseline or at 12- or 24-month early recalls. Cytology-negative HR-HPV positive women were referred at 24 months in case of infection persistence. A subset of cytology negative women was also referred at 12 months if they were infected with HPV 16/18.\textsuperscript{7} Cytology was read with knowledge of HR-HPV infections. Abnormalities were defined as an equivalent to atypical squamous cells of undetermined significance (ASCUS) or worse in the Bethesda 2014 classification. Women referred to early recall received an invitation before the new test was due. If no result was received, they received reminders and the laboratory informed their general practitioners (GP). Colposcopy referral was made to the clinic directly by the laboratory. If the woman defaulted the appointment, she could be re-referred or offered a second appointment before being discharged back to the GP.

### TABLE 1

| Description of all screened women and the study population with HR-HPV infections at baseline, by age, deprivation level and laboratory |
|---|---|---|---|---|
| Age (years) | Total | HR-HPV+\textsuperscript{a} | HR-HPV+/Cyt\textsuperscript{b} | HR-HPV+/Cyt–\textsuperscript{b} |
| 24–29 | 56 593 (19%) | 15 398 (27%) | 5982 (39%) | 9416 (61%) |
| 30–64 | 247 312 (81%) | 21 048 (9%) | 6226 (30%) | 14 822 (70%) |
| Deprivation | Low | 150 352 (49%) | 15 985 (11%) | 5026 (31%) | 10 959 (69%) |
| | High | 153 553 (51%) | 20 461 (13%) | 7182 (35%) | 13 279 (65%) |
| Laboratory | A | 36 733 (12%) | 5002 (14%) | 1619 (32%) | 3403 (68%) |
| | B | 30 387 (10%) | 3501 (12%) | 1475 (42%) | 2026 (58%) |
| | C | 33 983 (11%) | 3626 (11%) | 1546 (43%) | 2080 (57%) |
| | D | 107 764 (35%) | 11 711 (11%) | 4229 (36%) | 7482 (64%) |
| | E | 25 026 (8%) | 2547 (10%) | 687 (27%) | 1860 (73%) |
| | F | 70 012 (23%) | 10 039 (14%) | 2652 (26%) | 7387 (74%) |
| Total | 303 905 (100%) | 36 446 (12%) | 12 208 (33%) | 24 238 (66%) |

Abbreviations: Cyt, cytology; HR-HPV, high-risk human papillomavirus.
\textsuperscript{a}Denominator for proportions: total screened (N = 303 905).
\textsuperscript{b}Denominator for proportions: HR-HPV+ women in the same age/deprivation/laboratory category.
Data were retrieved from the laboratories’ information systems. This included each woman’s age, postcode and dates, outcomes and management codes of all cervical tests, including colposcopies, in the first (prevalence) round of screening with HR-HPV tests. Data were available from the beginning of the pilot in May 2013 until December 2018.

The woman’s postcode at the time of screening was linked to the English government indices of deprivation report from 2015, to identify Index of Multiple Deprivation (IMD) deciles. IMD is a standard relative indicator of deprivation used in England and measures aspects such as income, unemployment, education, crime, health and the living environment at a postcode level.

Screening tests were registered under the unique English NHS numbers. A prevalence episode was defined as the first episode per woman within the pilot. It was closed after the primary screening test if the result was negative and the outcome was for “routine recall”; in other cases, we added the intervening tests and colposcopies to the episode.

We collected information on any tests registered during a 2-year period preceding the pilot. If any such preceding test was registered, we excluded the first pilot test from further analysis, as it was most likely not taken for primary screening. Additionally, we excluded first tests if their management code suggested that they were taken as part of follow-up or at colposcopy.

**FIGURE 1** Flow chart of women screened with HR-HPV testing and their outcomes at baseline, and at 12- and 24-month early recall. The flowchart includes only those HR-HPV positive women who were referred in accordance with the pilot recommendations. A small proportion of HR-HPV positive women were referred to other types of follow-up and were not included in this analysis.
### 2.4 | Statistical analysis

In total, 303,905 women with a known postcode were screened with HR-HPV testing for the first time at age 24 to 64 years in 2013 to 2015 and, if an infection was detected, had positive or negative cytology. Women aged 24 (N = 6745, 2%) were included because the first screening invitation is sent at 24.5 years. By December 2018, these women had 36 to 68 months of observation after the screening test, which should adequately cover the period with the two recommended early recalls and the associated colposcopies.

We studied the proportions of women among those referred who attended a colposcopy or early recall after having been screened with HR-HPV testing. Absolute deprivation-specific proportions of women with a given outcome were age standardised to reflect the age distribution (24-29 vs 30-64 years) among HR-HPV positive women. IMD deciles were categorised into more deprived (deciles 1-5) vs less deprived (deciles 6-10) areas. Deciles 1 and 2 vs deciles 9 and 10 were also compared in a sensitivity analysis to test robustness of the findings. The effect of deprivation on attendance was studied using odds ratios (OR) from logistic regression, and the models were adjusted for age and laboratory. In models studying the effect of deprivation, age was included as a continuous variable. In the main models studying the effect of age, age was categorised as 24 to 29 years vs 30 to 65 years to maintain meaningful numbers of older women who were referred to further investigations. Results categorising age as 24 to 29 vs 30 to 49 vs 50 to 64 years were reported separately. Since an OR cannot be interpreted as representing the size of the difference in attendance when this outcome is achieved by the majority of the population, we also calculated the relative proportions (RP) of those attending colposcopy or early recall by deprivation category or age group. The 95% confidence intervals (CI) for RP were calculated assuming that their logarithms were approximately normally distributed.

Among women who attended early recall, we studied the number of days between the initial screening date and attendance for the 12-month early recall, and between attendance for the 12-month and the 24-month early recalls. We created a cumulative density function and calculated the medians and interquartile (IQR) ranges, as the data were strongly positively skewed. Seventeen (0.1%) women did not have a known date of 12-month early recall and were excluded.

Analyses were undertaken in R version 3.5.1.

### 3 | RESULTS

About half of the 303,905 screened women were categorised as being from more deprived areas (deciles 6-10), 153,553 (51%) (Table 1). In total, 56,593 (19%) were aged 24 to 29 years at screening, 172,658 (57%) 30 to 49 and 74,654 (25%) 50 to 64, which is similar to the age distribution observed in the CSP.9

Of 36,446 HR-HPV positive women, 20,461 (56%) were from more deprived areas, and 15,398 (42%) were younger than 30. Younger HR-HPV positive women and those from more deprived areas were slightly more likely to have cytological abnormalities. There was
some variation in HR-HPV test outcomes between the laboratories, but it was confined to a relatively narrow range. Colposcopy referral was made at baseline for 12,203 cytology-positive women, while 24,098 were cytology negative and recommended for 12-month early recall (Figure 1). Among those who attended the 12-month early recall, 7,061 were referred for early recall at 24 months.

Overall, attendance at early recall was 86.1% at 12 months and 84.7% at 24 months. The difference in attendance between the more deprived and less deprived areas was statistically significant: ORadj at 12 months was 0.89 (95% CI: 0.83-0.96) and at 24 months was 0.76 (95% CI: 0.67-0.87) (Table 2). However, the absolute differences were small. Among women from the more deprived areas, 85.6% attended at 12 months and 83.0% attended at 24 months (age-standardised) (Figure S1). Among those from the less deprived areas, this was 86.5% and 86.3%, respectively. The RPs for women from more deprived vs less deprived areas were 0.98 (95% CI: 0.97-0.99) at 12 and 0.96 (95% CI: 0.94-0.98) at 24 months.

The median time taken to attend 12-month early recall was around 13 months (391 days, IQR: 363-498) with only slight differences by deprivation: in the less deprived areas the time taken was 386 days (IQR: 363-482), and in the more deprived areas it was 394 days (IQR: 364-518) (Figure 2). Those invited for 24-month early recall attended a median of 386 (IQR: 362-473) days after the 12-month early recall, again with only very slight differences by deprivation: 386 (IQR: 362-463) in the less deprived vs 388 (IQR: 361-479) days in the more deprived areas.

Over 90% of the referred women attended colposcopy. After baseline colposcopy referral, 97% of women attended overall. Women were slightly less likely to attend if they were from a more compared with a less deprived area: 96.9%, vs 97.8% respectively, RP: 0.99 (95% CI: 0.98-1.00) and ORadj: 0.70 (95% CI: 0.55-0.88). The pattern for women invited to colposcopy after the 12- and 24-month early recalls was similar, with RPs of 0.98 (95% CI: 0.97-1.00) at 12 months and 0.97 (95% CI: 0.95-0.99) at 24 months; the ORadj at 12 months was 0.75 (95% CI: 0.58-0.98; 94.0% vs 95.6%) and at 24 months it was 0.80 (95% CI: 0.64-0.99, 89.3% vs 91.6%). The results in the sensitivity analysis in which we compared the extreme levels of IMD deprivation were very similar (Supplementary Information, Table S1).

When we compared age groups 24 to 29 and 30 to 64 years, we found that older women were significantly more likely to attend the 12-month early recall, ORadj: 1.33 (95% CI: 1.24-1.43; age-specific proportions: 87.5% among older vs 83.9% among younger women, RP: 1.04, 95% CI: 1.03-1.05), and at 24 months, ORadj: 1.32 (95% CI: 1.16-1.51; 86.1% vs 82.3%, RP: 1.05, 95% CI: 1.02-1.07) (Table 3).
We found no statistically significant age-related difference in attendance at colposcopy. The patterns were very similar for women aged 30 to 49 and 50 to 64 years (Supplementary Information, Table S2). The differences were similarly small between the laboratories (Supplementary Information, Figure S2).

The differences between young women from more deprived areas and older women from less deprived areas, the two extreme groups suggested by Tables 2 and 3, tended to be relatively small (Table 4). Nevertheless, they were more pronounced at the 24-month early recall, when 81.3% and 88.2%, respectively, of the referred women attended.

### Table 3

| Age group (years) | N referred | N attended | Observed % | OR_{unadj} (95% CI) | OR_{adj} (95% CI) | RP_{unadj} (95% CI) |
|------------------|------------|------------|------------|----------------------|------------------|---------------------|
| Baseline colposcopy | Total       | 12 203     | 11 868     | 97.3%                | –                 | –                   |
|                  | 24–29      | 5979       | 5807       | 97.1%                | 1.00 (ref)        | 1.00 (ref)           |
|                  | 30–64      | 6224       | 6061       | 97.4%                | 1.10 (0.89-1.37)  | 1.10 (0.88-1.37)    |
| 12-month early recall | Total       | 24 098     | 20 754     | 86.1%                | –                 | –                   |
|                  | 24–29      | 9371       | 7863       | 83.9%                | 1.00 (ref)        | 1.00 (ref)           |
|                  | 30–64      | 14 727     | 12 891     | 87.5%                | 1.35 (1.25-1.45)  | 1.33 (1.24-1.43)    |
| Colposcopy after 12-month early recall | Total       | 4725       | 4475       | 94.7%                | –                 | –                   |
|                  | 24–29      | 2125       | 2019       | 95.0%                | 1.00 (ref)        | 1.00 (ref)           |
|                  | 30–64      | 2600       | 2456       | 94.5%                | 0.90 (0.69-1.16)  | 0.90 (0.70-1.17)    |
| 24-month early recall | Total       | 7061       | 5979       | 84.7%                | –                 | –                   |
|                  | 24–29      | 2718       | 2238       | 82.3%                | 1.00 (ref)        | 1.00 (ref)           |
|                  | 30–64      | 4343       | 3741       | 86.1%                | 1.33 (1.17-1.52)  | 1.32 (1.16-1.51)    |
| Colposcopy after 24-month early recall | Total       | 3935       | 3555       | 90.3%                | –                 | –                   |
|                  | 24–29      | 1478       | 1345       | 91.0%                | 1.00 (ref)        | 1.00 (ref)           |
|                  | 30–64      | 2457       | 2210       | 89.9%                | 0.88 (0.71-1.10)  | 0.90 (0.72-1.13)    |

Abbreviations: OR, odds ratios (adjusted for deprivation [five more deprived deciles vs five less deprived deciles] and laboratory); RP, relative proportions.

### Table 4

| Age group (years) | 24–29 y, more deprived areas | 24–29 y, less deprived areas | 30–64 y, more deprived areas | 30–64 y, less deprived areas |
|------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Baseline colposcopy | 96.8%                      | 97.6%                      | 97.0%                      | 97.9%                      |
| 12-month early recall | 84.2%                      | 83.5%                      | 86.5%                      | 88.7%                      |
| Colposcopy after 12-month early recall | 94.1%                      | 96.3%                      | 94.0%                      | 95.0%                      |
| 24-month early recall | 81.3%                      | 83.6%                      | 84.3%                      | 88.2%                      |
| Colposcopy after 24-month early recall | 90.4%                      | 91.7%                      | 88.5%                      | 91.5%                      |

We found no statistically significant age-related difference in attendance at colposcopy. The patterns were very similar for women aged 30 to 49 and 50 to 64 years (Supplementary Information, Table S2). The differences were similarly small between the laboratories (Supplementary Information, Figure S2).

The differences between young women from more deprived areas and older women from less deprived areas, the two extreme groups suggested by Tables 2 and 3, tended to be relatively small (Table 4). Nevertheless, they were more pronounced at the 24-month early recall, when 81.3% and 88.2%, respectively, of the referred women attended.

### 4 Discussion

In this routine screening setting, most HR-HPV positive women attended the recommended early recall, demonstrating that early recall is an effective strategy in managing women who screen HR-HPV positive with negative cytology. This allows for viral clearance, reduces the need for colposcopy and is safe. Our observation is much more favourable than has been observed in research studies. This may be due to endorsement of the recommendations by health professionals involved in screening, careful messaging developed to advise the women and a high degree of trust in the CSP. Attendance at early recall did not show a decline over time, with 14% missing their appointments at 12 months and 15% at 24 months, although a quarter of women presented with a delay of more than 4 months. Our data are consistent with those from research settings showing that by far the majority of HR-HPV positive women, 90% or more, do undergo a colposcopy if referred. There was a small increase in colposcopy non-attendance with each successive early recall, with 3% of the referred women not attending a colposcopy at baseline, 5% not attending after the 12-month early recall, and 10% not attending after the 24-month early recall. Despite the high rates, a further increase in
attendance would likely be beneficial. In the pilot’s prevalence round, HR-HPV testing detected 23 CIN2+ per 1000 screened women.\(^5\) Assuming the same prevalence of CIN2+ in women who did not present for early recall and/or colposcopy, we estimate that an additional 2 CIN2+ could be detected per 1000 screened if all women attended the recommended follow-up.

It is important that women’s results are communicated in a way that emphasises the need for follow-up attendance without causing undue anxiety in the interim. Evidence from the psychological evaluation of this pilot suggests women are less anxious following receipt of a second HR-HPV positive result (at 12-month early recall) than their first positive result.\(^10\) Although this is encouraging from the point of view of minimising adverse psychological impact, it is possible that lower anxiety is associated with lower attendance at follow-up.

Women from deprived areas are at higher risk of cervical cancer, not only because of a higher prevalence of risk factors, but also because they are less likely to attend primary screening.\(^11-13\) When it comes to following up on clinical recommendations after screening, the differences in nonattendance at colposcopy, by deprivation, are much less pronounced. In the pilot, these differences were indeed statistically significant, but size of the effect was small. In the more deprived areas, 3% defaulted from baseline colposcopy and 2% in the less deprived; at 12 months, 5% and 4% defaulted, respectively; at 24 months, the figures were 11% and 8%. Similarly, at the 12-month early recall the difference in default was 14% vs 13%, and at the 24-month early recall it was 17% vs 14%. We could not detect a “dose-response” relationship between the decile of deprivation and attendance. Likewise, young age does not appear to be a major contributor to non-attendance, although young women from more deprived areas were more likely to default from the 24-month early recall than older women from less deprived areas.

Among women screened in East England during 2006 to 2013, 7.5% defaulted from baseline colposcopy in the lowest and 5.9% in the highest income quintile, without a relationship between income quintile and attendance.\(^14\) In the UK-based TOMBOLA trial, default rates from colposcopy comparing those who do not have postschool education vs those who do were 9.5% and 6.1%, respectively. Default rates among those in full-time employment and those not in paid employment were 5.1% vs 11.3%.\(^15\) Among women in the same trial who were referred to early recall in 6 months, 3.6% of those with no post-secondary education defaulted compared with 1.4% among those with training through work/college.\(^16\) In Ontario, 58% of women in the lowest neighbourhood income quintile defaulted from a 6-month repeat test compared with 53% for women from the highest quintile.\(^17\) Although overall attendance may differ from context to context, our results are in line with these previous studies showing that there do not, in fact, seem to be major socioeconomic inequalities at play.

A strength of this analysis is that the English pilot is the largest study of routine implementation of HR-HPV testing in primary screening to date in Europe, with all recommendations and processes representative of what is to be expected once HR-HPV testing is rolled out nationally. A limitation of the study is that although registration of early recall and colposcopy was highly complete, women could not be traced if they moved to a nonpilot area. Additionally, postcode-level deprivation is not a perfect representation of deprivation at an individual level, but the information on the latter is not routinely collected in England.

## 5 CONCLUSIONS

The English pilot showed a high rate of attendance to the recommended management of HR-HPV infections. Despite being statistically significant, the effects of deprivation and age were small. Communicating with young women and those from deprived areas about the benefits of attending follow-up may be helpful, but policies aiming to improve the overall attendance should not focus only on these two factors.

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## CONFLICT OF INTEREST

LG: No conflict of interest to disclose. CSM: Holds an honorary appointment at Public Health England to process the data for the pilot. JW: Public Health England provided financing for the psychological evaluation of the pilot. HK: Former chair of the Advisory Committee for Cervical Screening (Public Health England), but the views expressed in this manuscript are those of the author and do not represent the view of Public Health England. MR: Public Health England provided financing for the epidemiological evaluation of the pilot; attended meetings with various HPV assay manufacturers; fee for lecture from Hologic paid to employer.

## DATA AVAILABILITY STATEMENT

No additional unpublished data are available from the authors. Requests for access to data should be made to Public Health England, Office for Data Release.

## ETHICS STATEMENT

Women participating in the HPV primary screening pilot were invited to make an informed choice on participating in the cervical screening programme. A decision is made to accept or decline a screening test based on access to accurate and up-to-date information on the condition being screened for, the testing process and potential outcomes. Specific information was provided at the invitation stage allowing for
personalised informed choice. There was further opportunity to reflect on what the test and its results might mean when they attended for screening with the clinician taking the sample. Regulation 5, Health Service Regulations 2002, Confidentiality Advisory Group Reference: 15/CAG/0207, was the legal basis to process the data.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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