Acceleration of cervical cancer diagnosis with human papillomavirus testing below age 30: Observational study

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Abstract
Several international cervical screening guidelines advise against using high-risk human papillomavirus (HR-HPV) testing in women younger than 30. The rationale for this in young women, lies in the potential for additional detection of both low-grade and high-grade cervical intraepithelial neoplasia (CIN) leading to unnecessary treatments without reducing the burden of cervical cancer. We studied 56 544 women screened at 24 to 29 with HR-HPV testing and 116 858 screened with liquid-based cytology (LBC) in the English HPV screening pilot. They were compared to 528 460 women screened at the age of 30 to 49. We studied the detection of cervical cancer and CIN2/3 across two consecutive screening rounds 3 years apart. At 24 to 29, a positive HR-HPV test detected more cases of cervical cancer in the prevalence round than did a positive LBC test (1.36/1000 screened vs 0.82/1000, ORadj: 1.61, 95% CI: 1.18-2.19). In women with a negative HR-HPV test, cervical cancer was diagnosed before or at the incidence round in 0.07/1000. After a negative LBC test, cancer detection reached 0.47/1000 and 40% of these cases were diagnosed at FIGO stage IB+. HR-HPV testing increased the detection of CIN2/3 diagnoses in two consecutive rounds combined by 30% (71.9/1000 vs 55.2/1000). The patterns of detection of cervical cancer and CIN2/3 were almost identical at older ages. These data support using HR-HPV testing for screening of women younger than 30, which not only accelerates the diagnosis of cervical cancer but leads to a similar relative increase in CIN2/3 diagnosis to that found in women aged 30 to 49.

KEYWORDS
cervical cancer, cervical intraepithelial neoplasia, cytology, high-risk human papillomavirus testing, mass screening
What's new?
The new data from this large population-based study convincingly demonstrate that HPV testing as a stand-alone cervical screening test, can accelerate the diagnosis of cervical cancer compared with liquid-based cytology. Using our protocol this was achieved while maintaining the increased detection of CIN2/3 at a level similar to that seen in women screened age 30-49. These results should stimulate policy makers to re-consider HPV testing below age 30.

1 | INTRODUCTION

High-risk human papillomavirus (HR-HPV) testing is more sensitive than cytology for cervical screening.1 This test allows extended screening intervals,2 and is more rational in a post-vaccination era. Its use, however, remains controversial for women younger than 30. In the United States, the American Cancer Society endorsed stand-alone HR-HPV testing for these women in late 2020 following encouraging findings from an unpublished modelling study; The American College of Obstetricians and Gynecologists accepted HR-HPV testing for young women in 2021 but explicitly stated that cytology remains the preferred test; while the US Preventive Services Taskforce continues to advise against HR-HPV testing before the age of 30.5 In Europe, HR-HPV testing is used for screening of women younger than 30 in countries like England, Scotland and Wales.6,7 In other organised screening programmes that offer screening to women younger than 30, for example, in Italy,8 Denmark9 and most of Sweden,10 HR-HPV testing remains reserved for women older than 30. The latter is supported by the guidelines published by the European Commission.11

This controversy stems from the lack of high-quality observational data for the age group, particularly in terms of cancer development.12 So far, most of the evidence supporting the use of HR-HPV testing has been derived from randomised controlled trials that reported outcomes across two consecutive screening rounds.1 These trials included ~94 000 women tested for HR-HPV and ~81 000 women tested with cytology, but very few of those were younger than 30. Within this context, some authoritative voices have argued that HR-HPV positive but cytologically negative high-grade cervical intraepithelial neoplastic lesions (CIN2/3) are unlikely to progress to cancer before age 30, so their detection could be delayed until women turn 30.5,10,11,13 The perceived absence of clinical benefit has been compounded by the concern about the high proportions of women with positive HR-HPV tests undergoing colposcopy and the high likelihood of CIN “overdiagnosis.” The latter has been based on the findings from a single randomised trial, where HR-HPV testing at age 25 to 29 detected almost four times as many CIN2 and more than twice as many CIN2/3 in two consecutive rounds than did (conventional) cytology.14 It is, however, unclear whether these findings are representative of other screening programmes, as the trial showed the highest relative detection with HR-HPV testing at any age out of all trials, that is, its cytology missed the highest numbers of CIN2+.15

We used data from a large English screening pilot to study the outcomes of HR-HPV testing and liquid-based cytology (LBC) across two consecutive screening rounds in 173 402 women younger than 30.16 These women were compared to 528 460 women aged 30 to 49, for whom HR-HPV testing has been universally endorsed.

2 | MATERIALS AND METHODS

2.1 | The English HPV pilot

The pilot has been previously described in detail.16-18 Briefly, six National Health Service (NHS) LBC screening laboratories in England using ThinPrep (Hologic) and SurePath (BD) systems converted about a third of their operations to HR-HPV testing using cobas 4800 (Roche), APTIMA (Hologic) and RealTime (Abbott) HR-HPV assays. These HR-HPV assays target the following genotypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. Each laboratory used both LBC and HR-HPV testing for primary screening, and selected administrative areas for the conversion to HR-HPV testing in a non-randomised process to ensure consistency of clinical recommendations for each health care provider. Generally, the allocation of screening tests was preserved over two consecutive rounds. Some LBC areas, however, converted to HR-HPV testing earlier than planned to resolve national backlogs owing to an increasing shortage of cytology workforce.19,20

Women aged 25 to 49 were invited for screening every 3 years. They were managed as described in Figure 1. The pilot followed the English Cervical Screening Programme’s (CSP) screening and colposcopy quality assurance guidelines.

2.2 | Data sources

Data on screening tests, colposcopies and the associated screen-detected diagnoses in 2013 to 2019 were retrieved from the laboratories’ information systems. Data on cervical cancer diagnoses and the registered CIN3 diagnoses in 1995 to 2018 were retrieved from the English National Cancer Registration and Analysis Service (NCRAS).21 English NHS numbers were used for linkage.
2.3 Statistical analysis

Women were categorised according to their age (24 to 49 years) at screening in the pilot’s first (prevalence) round. We included women aged 24 because the first CSP screening invitation is sent at 24.5 years. Women older than 49 years were not included as their routine recall interval is 5 years.

We included screening episodes in the pilot’s prevalence round in 2013 to 2015, and any subsequent (incidence) episodes that started by the end of 2018 after negative prevalence-round screening tests.
In the absence of reliable information on the reason for taking a sample, and to exclude women whose first pilot samples were most likely made for follow-up of a recent abnormality, we excluded women if their first pilot sample was preceded by any NCRAS cervical cancer record or by an NCRAS CIN3 record in the previous 3 years, any LBC or HR-HPV test in the past 2 years or the baseline sample's management code reported that it was taken as part of follow-up or at colposcopy. All records for each woman were ranked by their dates to determine the sequence of primary, early recall and diagnostic events within each episode.

We determined the age-specific detection of squamous or glandular cervical cancer and CIN2/3. Throughout this analysis, information on CIN diagnoses made during the pilot was based on the laboratory data, while the source of data on cervical cancers was NCRAS. Cancers were stratified into FIGO stages IA vs IB+ vs unknown. The detection was observed for LBC and HR-HPV testing separately after a positive test in the prevalence round, and, for all women with a negative test in the prevalence round, either before the incidence round (where cervical cancers are usually diagnosed following symptoms or other clinical concerns) or after a positive test at incidence-round screening 3 years later.

We could not estimate the cumulative detection of lesions across the two screening rounds using traditional approaches such as, for example, by summing the counts from each round. This was because 29% of the women attending the incidence round after a prevalence-round LBC screen were tested for HR-HPV owing to the early conversion to HR-HPV testing in some LBC pilot areas (see above). Including incidence-round lesions from these women in the counts would overestimate the cumulative detection for LBC and make HR-HPV testing TABLE 1 Observed numbers of CIN2, CIN3 and cervical cancer diagnoses in the prevalence and incidence screening rounds, by age in the prevalence round and the type of the screening test

| Age in the prevalence round episode (years) | 24 to 29 | 30 to 39 | 40 to 49 |
|---------------------------------------------|---------|---------|---------|
| N Per 1000 (95% CI)                         | N Per 1000 (95% CI) | N Per 1000 (95% CI) |
| **HR-HPV testing**                          |         |         |         |
| Prevalence round                            |         |         |         |
| N                                           | 56 544  | 81 660  | 91 077  |
| CIN2                                        | 1478    | 793     | 332     |
| CIN3                                        | 2247    | 1245    | 419     |
| Cancer, screen+                             | 77      | 78      | 46      |
| (of which ER)a                              | 19      | 15      | 2       |
| Cancer, screen−                             | 2       | 0       | 6       |
| Incidence round                             |         |         |         |
| N                                           | 25 107  | 47 712  | 59 919  |
| CIN2                                        | 107     | 98      | 61      |
| CIN3                                        | 90      | 67      | 28      |
| Cancer, screen+                             | 1       | 0       | 0       |
| **LBC**                                     |         |         |         |
| Prevalence round                            |         |         |         |
| N                                           | 116 858 | 173 504 | 182 219 |
| CIN2                                        | 1724    | 923     | 428     |
| CIN3                                        | 3064    | 1635    | 598     |
| Cancer, screen+                             | 96      | 118     | 72      |
| Cancer, screen−                             | 13      | 16      | 18      |
| Incidence round                             |         |         |         |
| N                                           | 44 842  | 78 357  | 91 543  |
| CIN2                                        | 280     | 183     | 126     |
| CIN3                                        | 545     | 301     | 99      |
| Cancer, screen+                             | 21      | 19      | 13      |

Note: Inclusion criteria in the incidence round: a negative screening test in the prevalence round (that started from the beginning of the pilot in 2013 and before the end of 2015) and the same type of the screening test in the incidence round (that started by the end of 2018). Abbreviations: Cancer, invasive cervical cancer (FIGO stage IA1 or above); CI, confidence interval; CIN, cervical intraepithelial neoplasia; ER, early recall; HR-HPV, high-risk human papillomavirus; LBC, liquid-based cytology; screen+, screening test was non-negative; screen−, screening test was negative. *HR-HPV positive women were recommended for an early recall if they had negative triage cytology, see Figure 1.
appear more favourable in comparison. Hence, we only included incidence-round episodes if women were screened with the same test in both rounds. The cumulative detection across two rounds was then estimated as follows. First, the detection was calculated as a proportion per 1000 women included in the analysis of each round separately. Thereafter, the round-specific proportions were summed, while weighting the detection in the incidence round by the attendance at the incidence round. Without weighting, the assumption of 100% compliance with repeated screening rounds would overestimate the cumulative detection, particularly for the screening test with the larger detection in the incidence round (usually LBC). The weights (attendance at the incidence round) were 77.3% at age 24 to 29, 81.3% at 30 to 39 and 83.3% at 40 to 49. These were observed from prevalence episodes starting in 2013 to 2014, with incidence rounds starting anytime until the end of 2019.

The analysis described above provides estimates for the cumulative detection of lesions across two screening rounds 3 years apart, as has been commonly done in the analyses of trial data.\textsuperscript{14,23} In general, however, HR-HPV testing allows for less frequent screening and the plan in the English CSP is to extend the routine recall interval for women younger than 50 from 3 years after negative LBC to 5 years after a negative HR-HPV test. Accounting for fewer HR-HPV screening rounds would provide a more informative estimate of the cumulative excess detection of high-grade CIN and the excess frequency of other events such as positive screening tests and colposcopies. We estimated this as follows. Using LBC, the English CSP invited women for the first two screens around the ages of 25 and 28. With HR-HPV testing, women will be invited for the second round only around age 30. We therefore assessed the differences in the cumulative numbers of screening tests, positive screening tests, colposcopy referrals and CIN2/3 diagnoses after the first two LBC screening rounds (with a pilot prevalence round around age 25, defined as 24 to 26 years and the corresponding incidence round) compared to one HR-HPV round around age 25. As above, we accounted for the fact that only a proportion of women attending the prevalence round also attended the incidence round. For women screened in the pilot at 25, this was 74.4%. To avoid comparing groups of different sizes, the absolute numbers of events with HR-HPV testing were recalculated to the number of women who were screened with LBC in the prevalence round.

In sensitivity analyses, we stratified the data for women younger than 30 into age groups 24 to 26 and 27 to 29 years; we reported the outcomes for HPV DNA assays separately; provided information on the cumulative frequencies of positive tests and colposcopy referrals; and reported the positive predictive value (PPV) of a colposcopy referral for CIN2\textsuperscript{+} and CIN3\textsuperscript{+}. Examples for all calculations are provided in Supporting Information. Absolute detection rates were reported with exact binomial 95% confidence intervals (CI). Age-specific odds ratios (ORs) comparing HR-HPV testing and LBC were calculated using logistic regression. They were adjusted for index of multiple deprivation decile.\textsuperscript{24}

### Table 2

Stage at diagnosis for cancers detected in women with positive and negative screening tests in the prevalence round, per 1000 screened

| Age group (years) and FIGO stage | HR-HPV testing | LBC |
|----------------------------------|----------------|-----|
|                                  | Positive test (per 1000 screened) | Negative test\textsuperscript{*} (per 1000 screened) | Total (per 1000 screened) | Positive (per 1000 screened) | Negative\textsuperscript{*} (per 1000 screened) | Total (per 1000 screened) |
| 24-29                            | 54 (0.96) | 1 (0.03) | 55 (0.99) | 59 (0.50) | 19 (0.28) | 78 (0.79) |
| 30-39                            | 78 (0.96) | 0 (0) | 78 (0.96) | 118 (0.68) | 35 (0.29) | 153 (0.97) |
| 40-49                            | 78 (0.96) | 0 (0) | 78 (0.96) | 118 (0.68) | 35 (0.29) | 153 (0.97) |

\textsuperscript{*}Combining cancer cases in women with a negative screening test in the prevalence round who were diagnosed before the incidence round and women with a negative screening test in the prevalence round who were diagnosed after a positive screening test in the incidence round, after accounting for attendance at the incidence round.

Abbreviations: FIGO, International Federation of Gynaecology and Obstetrics; HR-HPV, high-risk human papillomavirus; LBC, liquid-based cytology.

\textsuperscript{1416}
is a standard English postcode-based measure of deprivation and laboratory site. Analyses were undertaken using R v3.6.1.

3 | RESULTS

HR-HPV testing was used in the prevalence round for 56,544 women aged 24 to 29, and LBC for 116,858 (Table 1). Data for the analysis of the incidence round were available for 25,107 and 44,842 women, respectively. Likewise, data were available for 528,460 women aged 30 to 49 screened with either test in the prevalence, and 277,531 women in the incidence round. Incidence rounds took place a median of 37 months after the prevalence rounds (mean: 38, interquartile range: 36-40).

3.1 | Detection of cervical cancer

After a positive LBC test at age 24 to 29 in the prevalence round, 96 (0.82/1000 screened) women had a cancer diagnosis (Table 1). In women with negative LBC, 0.47/1000 were diagnosed with cancer before (n = 13) or at (n = 21) the incidence round (Table 2). Of these initially LBC negative cancers, 40%, or 0.19/1000 screened, were diagnosed at stage IB+ (about a quarter of which at stage II+; not tabulated). Across two LBC screening rounds combined, 1.29/1000 had a cancer diagnosis, among whom 0.44/1000 were stage IB+.

Among women aged 24 to 29, 77 (1.36/1000) received a cancer diagnosis after a positive HR-HPV test in the prevalence round; this was 61% (95% CI: 18-119) more cancer diagnoses than observed with LBC (Table 3). About one in four of these HR-HPV positive cancers initially presented with negative triage cytology and was diagnosed at early recall with persistently positive HR-HPV tests, the majority at 12 months (Table 1). After a negative HR-HPV test, 0.07/1000 women were diagnosed with cancer before (n = 2) or at the incidence round (n = 1); of these three cases, two were diagnosed at stage IB and none were diagnosed at stage II+. Across both rounds combined, 1.43 cancers were detected per 1000 women, with 0.35/1000 diagnosed at stage IB+ (Table 2).

The detection of cancer across two rounds decreased with age both after positive and negative screening tests (Tables 1 and 2). The patterns were, however, similar for all age groups: (a) a higher detection after a positive screen in the prevalence round with HR-HPV testing than with LBC (although not statistically significantly at 30 to 49;...
Tables 1-3, (b) a lower risk of cancer after a negative HR-HPV test than after negative LBC (Tables 1-3) and (c) a similar cumulative detection across two screening rounds for both screening tests (Table 2). The proportion of women who had a cancer diagnosed at stage IB+ after negative LBC was approximately the same below and above age 30 (range: from 0.14 to 0.19/1000, Table 2).

3.2 | Detection of CIN2/3

As expected, the detection of CIN2/3 was higher in the prevalence than in the incidence round and was higher in younger than in older women in both rounds (Table 1). In all age groups, the cumulative detection of CIN2/3 across two screening rounds 3 years apart, remained higher with HR-HPV testing (Table 4). At 24 to 29, HR-HPV testing detected 9.9/1000 or 50% more CIN2, and 6.9/1000 or 19% more CIN3 than LBC screening (30% more when CIN2 and CIN3 were combined). The increases in cumulative CIN2/3 detection achieved with HR-HPV testing were similar at older ages, 40% at 30 to 39 and 24% at 40 to 49. Adjustment for deprivation and laboratory site hardly changed any of the age-specific ORs comparing HR-HPV testing with LBC (Table 3).

3.3 | Two LBC screening rounds vs one HR-HPV round in women younger than 30

Among 60 996 women screened with LBC at 25, 106 374 primary screening tests were made across two screening rounds (Table 5). These two rounds resulted in 9247 positive tests and colposcopy

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**TABLE 5** Two rounds of screening with LBC vs one round of screening with HR-HPV testing, at 25 years of age. Estimated changes in the numbers of screening tests, positive screens, colposcopy referrals and detected CIN2/3 lesions

| Observed data per screening round | Prevalence round with LBC (per 1000) | Incidence round with LBC (per 1000) | Prevalence round with HR-HPV testing (per 1000) | LBC at 25 vs HR-HPV at 25, per 1000 (% change) |
|----------------------------------|--------------------------------------|-------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Age at screening (years)<sup>a</sup> | 25                                   | 28                                  | 25                                            | 25 vs 25                                      |
| Test type                        | One LBC                              | One LBC                             | One HR-HPV                                    | One LBC vs one HR-HPV                         |
| N women                          | 60 996                               | 22 872                              | 30 147                                        |                                              |
| N screens                        | 60 996                               | 22 872                              | 30 147                                        |                                              |
| Positive screening test          | 6785 (111.2)                         | 1241 (54.3)                         | 9564 (317.2)                                  | +206.0 (+185%)                                |
| Colposcopy referrals             | 6785 (111.2)                         | 1232 (53.9)                         | 6108 (202.6)                                  | +91.4 (+82%)                                  |
| CIN2/3                           | 2970 (48.7)                          | 527 (23.0)                          | 2333 (77.4)                                   | +28.7 (+59%)                                  |

**Estimated outcomes from the programme perspective associated with a change in interval**

| Twice LBC (per 1000)<sup>b</sup> | Once HR-HPV (per 1000)<sup>c</sup> | Twice LBC — once HR-HPV, absolute difference per cohort | Twice LBC — once HR-HPV, per 1000 (% change) |
|----------------------------------|-------------------------------------|---------------------------------------------------------|-----------------------------------------------|
| Age at screening (years)<sup>a</sup> | 25 + 28                             | 25                                                      | 25 vs 25 + 28                                 |
| Test type                        | Twice LBC                           | Once HR-HPV                                            | Once HR-HPV vs twice LBC                       | Once HR-HPV vs twice LBC                       |
| N women                          | 60 996                              | 60 996                                                 | −45 378                                       | (−43%)                                        |
| N screens                        | 106 374                             | 60 996                                                 | 9247 (151.6)                                  | 19 351 (317.2)                                |
| Positive screening tests         | 9247 (151.6)                        | 12 358 (202.6)                                        | +10 104                                       | +165.6 (+109%)                                |
| Colposcopy referrals             | 9292 (151.3)                        | 4720 (77.4)                                            | +3129                                          | +51.3 (+34%)                                   |
| CIN2/3                           | 4016 (65.8)                         | 4720 (77.4)                                            | +705                                           | +11.6 (+18%)                                   |

Abbreviations: CIN, cervical intraepithelial neoplasia; HR-HPV, high-risk human papillomavirus; LBC, liquid-based cytology.

<sup>a</sup>Age 25: women who were aged 24 to 26 at the time of screening in the prevalence pilot round. Age 28: age in the incidence round, after a negative LBC screen at age 24 to 26 years in the pilot’s prevalence round. This was around age 28 (estimated as 27-29), as the median time from the baseline screen in the prevalence round to the baseline screen in the second round was 37 months (interquartile range: 36-40).

<sup>b</sup>Screens at ages 25 and 28 years combined, taking into account that 74.4% of women aged around 25 years screened after the first CSP invitation attend screening after the second invitation.

<sup>c</sup>Observed results recalculated for a cohort of 60 996 women, that is, the number who were screened with LBC at 25 in the prevalence round.
referrals, and 4016 CIN2/3 diagnoses. Based on our data, a single round of HR-HPV testing would result in 43% fewer screening tests, 109% more positive tests, 34% more colposcopy referrals and 18% more CIN2/3 diagnoses.

3.4 | Sensitivity analyses

With the 3-year routine recall interval, women aged 24 to 26 were typically invited for an incidence round before they turned 30, while those aged 27 to 29 were reinvited after they turned 30. Both age groups, however, showed similar patterns in terms of the excess detection of high-grade CIN and cervical cancer with HR-HPV testing compared to LBC (Tables S1-S3). Likewise, the results remained virtually the same when only laboratories with HPV DNA testing were included in the analysis (Tables S4-S6; the two mRNA laboratories were too small to provide reliable age-specific results).

Finally, we repeated the analyses to determine the cumulative frequencies of women with positive screening tests and colposcopy referrals (Tables S7-S9). As with all other outcomes, these were highest at younger ages, but the proportional increases after HR-HPV testing compared to LBC were larger at older ages. This pattern did not change when we included only women with at least CIN1 diagnosed at colposcopy. The PPV for either CIN2+ or CIN3+ were higher at younger ages regardless of the screening test.

4 | DISCUSSION

This large observational study undertaken within the context of the quality-assured English CSP, has shown that the balance between the clinical benefits and the harms of HR-HPV testing in women younger than 30 is more favourable than has been considered so far. Women aged 24 to 29 were more likely diagnosed with cervical cancer after negative LBC than older women, while HR-HPV testing resulted in fewer delayed diagnoses which emerged in the years after negative LBC. A single round of HR-HPV testing roughly replacing two rounds of LBC under the age of 30, as planned within the English CSP, would increase colposcopy referrals from 15.1% to 20.3% of screened women aged 24 to 29 were more likely diagnosed with cervical cancer after negative LBC than older women, while HR-HPV testing resulted in the detection of CIN2/3 diagnoses. The PPV for either CIN2+ or CIN3+ were higher at younger ages regardless of the screening test.

HR-HPV negative women. Although based on small numbers, this may be suggestive of interval progression to more advanced FIGO stages in LBC negative cancers before age 30.

Furthermore, much like at older ages a negative HR-HPV test at a young age was associated with a very low 3-year risk of CIN3 and cervical cancer. With HR-HPV testing, these lesions were diagnosed predominantly in the prevalence round, whereas with LBC they were more uniformly distributed across the two rounds. This confirms the safety of extended HR-HPV screening intervals for all participants including those who undergo screening irregularly. In the pilot, about a quarter of women screened at 25 did not attend the next round for 5 years or longer.

The increases in colposcopy referrals and high-grade CIN diagnoses at a young age are frequently discussed harms of HR-HPV testing. Although our data showed that HR-HPV testing increases the relative detection of CIN2 more than it increases the relative detection of CIN3, these harms are overestimated when the opportunity to extend screening intervals is not taken into account. Conservative criteria for a referral of HR-HPV positive women with negative cytology and careful selection for treatment after a diagnosis of CIN2 would further diminish the harms of HR-HPV screening under the age of 30. In the pilot and within the English CSP, colposcopy referral required evidence of viral persistence for at least 12 months after screening; histologically confirmed CIN2/3 are usually treated, although CIN2 is sometimes also managed conservatively. Nevertheless, even after accounting for longer screening intervals, our data still suggested a doubling of the numbers of women with a positive screening test under the age of 30. This may carry a risk of adverse psychological consequences.

The strength of our data is their size, incorporating more than twice as many women screened with HR-HPV testing as all randomised trials combined, with detailed screening information and a link to the national cancer register where diagnostic FIGO stages were known in more than 90% of the cases. The pilot was embedded within the national CSP and was subject to the same quality assurance as routine cervical screening. A limitation was that the allocation of screening tests was not randomised. Small differences in age and area deprivation between women undergoing HR-HPV testing and those screened with LBC had no practical consequences for the comparison of screening outcomes (Table 3), although some degree of residual confounding could not be excluded. Finally, the analysis included data from the first two rounds of screening with HR-HPV testing. This is a short period compared to the time it takes for CIN to progress to cancer. It is therefore not surprising that we could not yet detect a reduction in the frequency of cancer diagnoses derived from detecting more HR-HPV-positive but cytology-negative CIN2/3 in any of the studied age groups. As in randomised trials, it is likely that this reduction will only be measurable after several more years.

The national HPV vaccination programme, which was initiated in England in 2008 with greater than 80% coverage, will exert a highly significant impact on the risk of cervical cancer, which will affect the efficiency of screening and will require changes to the programme if its cost-effectiveness is to be maintained. Although most screening programmes have not yet revised screening recommendations for vaccinated women, cost-effective measures would include longer...
screening intervals and a later starting age (potentially at age 30 or later).36,37

In conclusion, data from the English pilot provide evidence that the increased sensitivity of HR-HPV testing in women younger than 30 promotes earlier diagnosis of cervical cancer without creating a large strain on colposcopy services. This new evidence calls for a reassessment of screening guidelines that recommend withholding HR-HPV testing from young women in favour of continued screening with LBC.

ACKNOWLEDGEMENTS

Access to the data used in this article was facilitated by the Public Health England’s Office for Data Release. The laboratory data were based on information collected and quality assured by the Public Health England Population Screening Programmes. The cancer diagnosis data were collated, maintained and quality assured by the National Cancer Registration and Analysis Service and the Public Health England Population Screening Programmes, which are part of Public Health England. This work used data that had been provided by patients and collected by the NHS as part of their care and support.

Members of the HPV Pilot Steering Committee, other than those listed as authors, included (in alphabetical order): Tracey-Louise Appleyard, Margaret Cruikshank, Kate Cuscieri, Karin Denton, Kay Ellis, Chris Evans, Viki Frew, Thomas Giles, Alastair Gray, Miles Holbrook, Katherine Hunt, Tanya Levine, Emily McBride, David Mesher, Timothy Palmer, Janet Parker, Elizabeth Rimmer, Hazel Rudge Pickard, Alexandra Sargent, David Smith, John Smith, Kate Soldan, Ruth Stubbs, John Tidy, Xenia Tyler, Jo Waller.

CONFLICT OF INTEREST

Matejka Rebolj: Member of the Public Health England Laboratory Technology Group and HPV Self-sampling Operational Steering Group and Project Board; attended meetings with various HPV assay manufacturers; fee for lecture from Hologic paid to employer. Christopher S Mathews: Holds an honorary appointment at Public Health England to process the data for the pilot. Francesca Pesola: Declares no conflict of interest. Alejandra Castañon: Consulted for Douglas Pharmaceuticals Ltd providing advice on study design; member of the Public Health England Cervical Screening Research Advisory Committee. Henry Kitchener: Former chair of the Public Health England Advisory Committee for Cervical Screening.

AUTHOR CONTRIBUTIONS

Conceptualisation and methodology: Matejka Rebolj, Alejandra Castañon, Henry Kitchener. Data management: Christopher S Mathews. Formal analysis: Matejka Rebolj, Francesca Pesola. Writing (original draft): Matejka Rebolj. Writing (review and editing): all authors. Decision to submit: all authors.

DATA AVAILABILITY STATEMENT

The data belong to the former Public Health England and the authors cannot provide access to the relevant datasets to third parties. Requests for data and pre-application advice should instead be made to Office for Data Release (odr@phe.gov.uk). Further details and other data that support the findings of our study are available from the corresponding author upon request.

ETHICS STATEMENT

The study was considered the first stage in national implementation, so it was referred to as an implementation pilot and therefore exempt from ethics approval. 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 in the online version of the article at the publisher’s website.

How to cite this article: Rebolj M, Mathews CS, Pesola F, Castanon A, Kitchener H, HPV Pilot Steering Group. Acceleration of cervical cancer diagnosis with human papillomavirus testing below age 30: Observational study. Int J Cancer. 2022;150(9):1412-1421. doi:10.1002/ijc.33900