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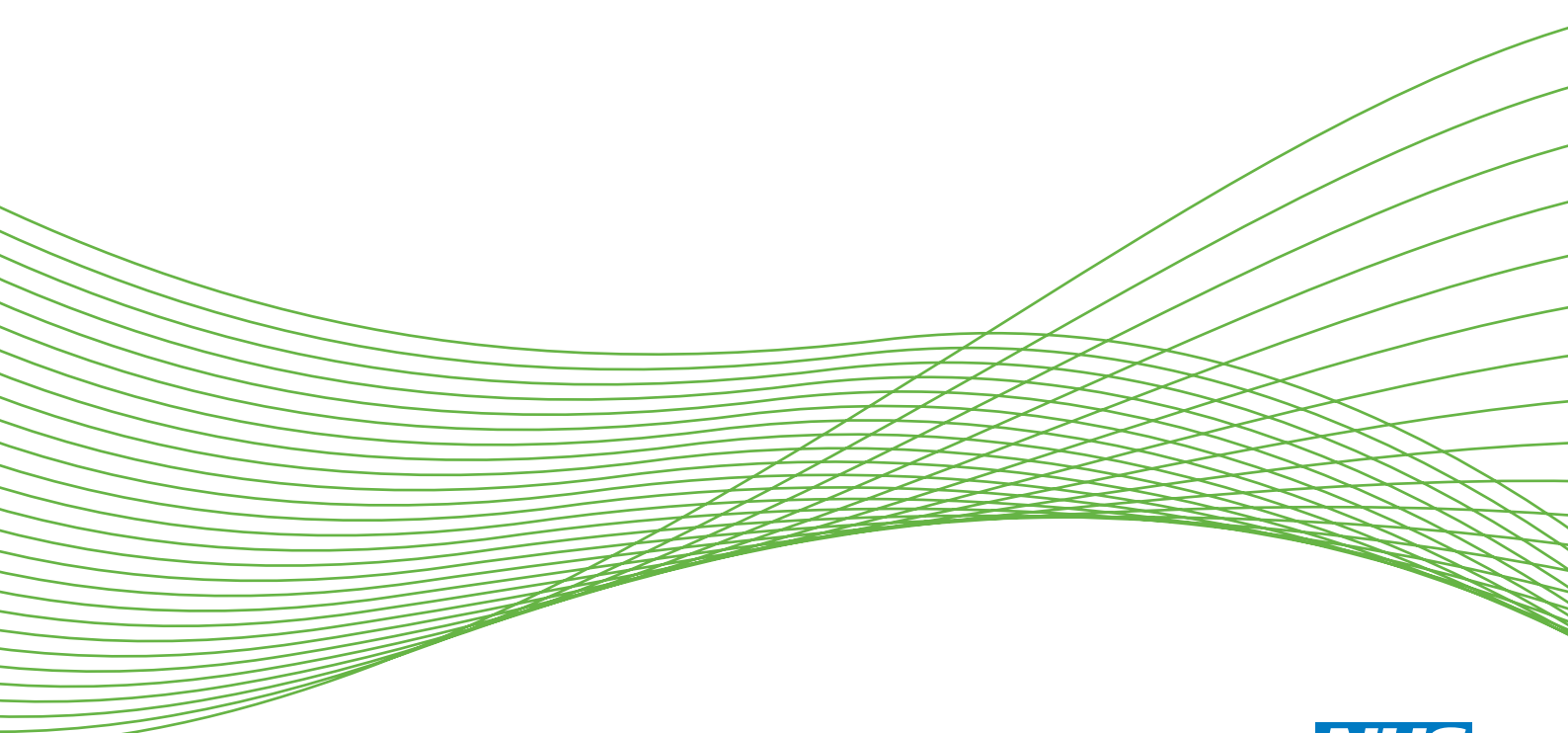
National Institute for Health Research

HPV testing compared with routine cytology in cervical screening: long-term follow-up of ARTISTIC RCT

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This report

Abstract

HPV testing compared with routine cytology in cervical screening: long-term follow-up of ARTISTIC RCT

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Background: The National Screening Committee (NSC) based its recommendation that human papillomavirus (HPV) testing should replace cytology in primary cervical screening largely on the 2009 follow-up results of the ARTISTIC trial (A Randomised Trial In Screening To Improve Cytology). The NSC must now decide on screening intervals and triage policy. Options include extending the screening interval up to 10 years for human papillomavirus-negative (HPV–) women, delaying recall for human papillomavirus-positive (HPV+) women with normal cytology (as their infections are usually transient), and basing triage on full HPV typing.

Methods: In ARTISTIC, 24,510 women were recruited who were attending routine cervical cytology in Greater Manchester in 2001–3. The women were randomly allocated between revealing and concealing their HPV test results and were recalled every 3 years. After 2009, the women returned to routine cytological screening with recall every 3 years for those aged < 50 years, and every 5 years for those aged 50–64 years. We have followed the cohort to 2015 through national cancer registration for CIN3 (cervical intraepithelial neoplasia grade 3) and cancer, and through linkage to the cervical screening call–recall system to obtain lifetime cytology records.

Results: The analysis comprised 24,496 women at round 1 and 13,591 women at round 2 (which was 30–48 months later). Follow-up via local histology laboratories and national cancer registration identified 505 cases of cervical intraepithelial neoplasia grade 3 or cervical cancer (CIN3+) (including 22 invasive cervical cancers). The cumulative CIN3+ risk 10 years after a negative HPV test [0.31%, 95% confidence interval (CI) 0.18% to 0.49%, in the revealed arm] was similar to that 3 years after negative cytology (0.30%, 95% CI 0.23% to 0.41%, in the concealed arm) and fell sharply with age, from 1.1% (95% CI 0.7% to 1.8%) in those women aged < 25 years to 0.08% (95% CI 0.03% to 0.20%) in those women aged > 50 years. The 10-year cumulative CIN3+ risk following a new HPV infection at round 2 was 3.4% (95% CI 2.1% to 5.4%). The highest risks were associated with type-specific persistent infections that, overall, resulted in a 10-year cumulative CIN3+ risk of 20.4% (95% CI 15.6% to 26.4%).

Conclusions: We found a similar level of protection 10 years after a negative HPV test and 3 years after negative cytology. These data support a considerably longer screening interval after a negative HPV test than after a negative cytology test. About three-quarters of women with HPV infection and normal cytology clear their infections within about 3 years. Their risk of CIN3+ within this time frame is low (1.5%), suggesting that the current policy of annual repeat testing and referral after 2 years may be unnecessarily cautious. Approximately 40% of women who remained HPV+ had cleared their initial infection and acquired

a new HPV type. The cumulative CIN3+ risks in women with type-specific persistent infections are about six times higher than in women with new infections. Triage strategies based on HPV persistence would, therefore, reduce unnecessary referral of women with new (and largely transient) infections. HPV assays that identify HPV types 31, 33, 45, 52 and 58 in addition to 16 and 18 could be useful in triage as well as in primary HPV testing. Similar results in recent routine HPV screening suggest that our results are generalisable despite changes in cytology and HPV assay methods. We are continuing to follow the ARTISTIC cohort into the new era of primary HPV screening. Future work will focus on the implications of more sensitive HPV testing for primary HPV screening policy and triage of HPV-positive women. Our results suggest that a more sensitive test is needed to detect occult CIN3 at high risk of progression to cancer, but this would substantially increase the overall HPV detection rate. Tests such as DNA (deoxyribonucleic acid) methylation for distinguishing HPV infection from neoplasia will be evaluated on stored samples and on further samples now being collected from women in the cohort who are still being screened.

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List of abbreviations

ARTISTIC	A Randomised Trial In Screening To Improve Cytology	HPV	human papillomavirus
CI	confidence interval	HPV−	human papillomavirus negative
CIN	cervical intraepithelial neoplasia	HPV+	human papillomavirus positive
CIN2+	cervical intraepithelial neoplasia grade 2 or worse	HRHPV	high-risk human papillomavirus
		LBC	liquid-based cytology
CIN3+	cervical intraepithelial neoplasia grade 3 or cervical cancer	NHSCR	NHS Central Register
DNA	deoxyribonucleic acid	NIHR	National Institute for Health Research
HC2	hybrid capture 2	NSC	National Screening Committee
HC2−	hybrid capture 2 negative	PCR	polymerase chain reaction
HC2+	hybrid capture 2 positive	RLU/Co	relative light units/mean control

Plain English summary

Human papillomavirus (HPV) causes cervical cancer. The latest scientific evidence shows that screening for HPV is better than screening for abnormal cytology with a 'smear' test, so HPV testing is being rolled out nationally. The main disadvantage is that more women will test positive and be referred for further tests. Most infections are harmless and clear without treatment, and balance must be achieved so that women who progress to CIN3 (pre-cancer) are identified but that unnecessary referral and anxiety for women is minimised.

A Randomised Trial In Screening To Improve Cytology (ARTISTIC) recruited 24,510 women attending for cervical screening in Greater Manchester in 2001–3. Cervical samples taken at recruitment and again at screening 3 and 6 years later were tested for HPV. The women then returned to routine screening. We have followed them through national screening records and cancer registration until the end of 2015.

By comparing the HPV results taken at entry with those collected 3 years later, we can categorise HPV infections into new and persistent. We have found that the CIN3 risk in women with persistent infections is about six times higher than in women with new infections, which in turn is about 30 times higher than in women with no infection.

About three-quarters of women with HPV infection but no abnormal cells clear their infections within 3 years. Their risk of pre-cancer within 3 years is low (1.5%) and so intensive follow-up is unnecessary. Moreover, 40% of those who remain human papillomavirus positive (HPV+) have cleared their initial infection and acquired a new infection, meaning that they are also at much lower risk of disease than those with a persistent infection. The current practice in the national pilot study of annual repeat testing and referral of anyone who is still HPV+ after 2 years may, therefore, be too conservative.

We have also shown that the CIN3 risk after 10 years in women testing negative for HPV is similar to the risk after about 3 years in women testing negative for cytology. This means that screening intervals could be extended for women testing negative for HPV.

Scientific summary

Background

The National Screening Committee (NSC) based its recommendation that human papillomavirus (HPV) testing should replace cytology in primary cervical screening largely on the 2009 follow-up results of A Randomised Trial In Screening To Improve Cytology (ARTISTIC) [URL: https://legacyscreening.phe.org.uk/cervicalcancer (accessed 19 April 2018)]. The NSC must now decide on screening intervals in time for national roll-out of primary HPV screening, currently scheduled for December 2019. Options include extending the screening interval for up to 10 years for human papillomavirus-negative (HPV−) women and delaying recall for human papillomavirus-positive (HPV+) women by up to 3 years if their cytology is normal, and perhaps by only 1 year if their cytology is borderline or mild. HPV infections are usually transient and a substantial reduction in triage costs and procedures could be achieved if a longer delay in patient recall was shown to be safe.

Methods

In ARTISTIC, 24,510 women attending for routine cervical cytology in Greater Manchester were recruited between 2001 and 2003. Cytology was conducted as part of the national screening programme using liquid-based cytology (LBC) technology and women with abnormal cytology were managed under national guidelines, irrespective of HPV results. Women were recalled twice, 3 and 6 years after entry. LBC samples at entry and at rounds 2 and 3 were tested for HPV and the residual material stored. Women were randomly allocated to reveal or conceal their HPV test results, and on the revealed arm women with normal cytology who were HPV positive were recalled after 1 year for a repeat HPV test. Histology results were obtained from local laboratories. After 2009, follow-up and sample collection ended and the women returned to routine cytological screening with recall every 3 years for those aged < 50 years and every 5 years for those aged 50–64 years. We have followed the trial cohort through national cancer registration for cervical intraepithelial neoplasia grade 3 (CIN3) and cancer, and through linkage to the cervical screening call–recall system for lifetime cytology records. Cumulative cervical intraepithelial neoplasia grade 3 or cervical cancer (CIN3+) risks were calculated comparing women according to HPV and cytology status at baseline. Additional analyses began at round 2, when persistent and newly acquired infections could be distinguished and the high prevalence of accumulated CIN3 missed by earlier screening had been eliminated at entry.

Results

The analysis comprised 24,496 women at round 1 and 13,591 women at round 2 (defined as the first test 30–48 months later). Follow-up was via local histology laboratories until 2009 when the trial ended and then via cancer registration until April 2015. This identified 505 cases of CIN3+ (including 22 invasive cancers). Similar cumulative CIN3+ risks were seen 10 years after a negative hybrid capture 2 (HC2) test at entry [0.31%, 95% confidence interval (CI) 0.18% to 0.49%, in the revealed arm] and 3 years after a negative cytology test at entry (0.30%, 95% CI 0.23% to 0.41%, in the concealed arm). The 10-year cumulative CIN3+ risk in women who were hybrid capture 2 negative (HC2−) at entry was highest in women aged 20–24 years (1.10%, 95% CI 0.69% to 1.77%) and significantly higher ($p < 0.001$) in women aged 25–39 years (0.40%, 95% CI 0.28% to 0.56%) than in those aged > 40 years (0.11%, 95% CI 0.06% to 0.20%).

The availability of partial or full HPV genotyping assays allows risk-based stratification in an organised screening programme. Four out of the six sites in the UK pilot study are utilising partial typing HPV tests [Roche COBAS (Roche Molecular Diagnostics, Pleasanton, CA, USA) and Abbott Realtime Assays (Abbott Molecular,

Maidenhead, UK)] that identify HPV 16 and HPV 18 infections. We found a much higher cumulative CIN3+ risk among women with HPV 16 infection than among women with any other genotype. Although HPV 16 constituted 22% of all hybrid capture 2-positive (HC2+) infections, 57% of CIN3+ occurred among this group of women, giving a 10-year cumulative CIN3+ risk of 29.8% (95% CI 26.8% to 33.0%). HPV 18 constituted 9% of all HC2+ infections (including 2% who also had HPV 16), with a 10-year cumulative CIN3+ risk similar to the group of high-risk HPV types comprising 31, 33, 45, 52 and 58.

The 10-year cumulative CIN3+ risk following a new high-risk HPV (HRHPV) infection at round 2 was low (3.4%, 95% CI 2.1% to 5.4%). HPV 16 again showed the highest 10-year risk following a new infection (7.3%, 95% CI 3.7% to 14.1%), suggesting that women with HPV 16 might be referred immediately. Much higher risks were associated with any type-specific persistence (the same HPV type as in round 1), which overall conferred a 10-year cumulative risk of 20.4% (95% CI 15.6% to 26.4%). The cumulative CIN3+ risk following type-specific persisting infection was similar regardless of age before the age of 40 years (23.8%, 95% CI 18.2% to 30.9%), but significantly lower ($p = 0.02$) in women aged ≥ 40 years (6.8%, 95% CI 2.3% to 19.7%). Persistent HPV 16 infections account for 44% of type-specific infections in those aged < 30 years and only 11% among women aged ≥ 40 years, but stratification by type does not entirely account for the reduction in CIN3+ risk in women aged ≥ 40 years. Of the 331 women with double positive HRHPV tests, 115 (35%) were positive with a new HPV type at the second test and 216 (65%) were type-specific persistent. The proportion with new infections was highest in younger women (43% in women in their 20s) and decreased to 23% of double positive infections in women aged ≥ 50 years. Entry samples for 17 out of the 23 cervical cancers diagnosed so far (including one diagnosed after the follow-up date) were HC2+. Five of the 6 HC2– entry samples were found to be HPV+ on retesting by PCR.

Conclusions

The CIN3+ risk 10 years after a negative HPV test is similar to that at 3 years after a negative cytology test. The risk at each age is approximately proportional to the incidence of new HPV infection in the population, which falls sharply with age and is very low in those aged ≥ 40 years. These data support a longer screening interval after a negative HPV test than after a negative cytology test. This could be at least 5 years, and might be extended to 10 years for women aged ≥ 50 years, or perhaps aged ≥ 40 years. About three-quarters of women with HPV infection and normal cytology clear their infections within 3 years. Their risk of CIN3+ within this time is low (1.5%), suggesting that the protocol in the national pilot of annual repeat testing [Public Health England. *HPV Primary Screening Pilot Protocol Algorithm*. Version 3.0. Public Health England; 2016. URL: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/529496/HPVPSFlowchart-Version3_Jan16.CURRENTppt.pdf (accessed 19 April 2018)] and referral after 2 years may be too conservative. Approximately 40% of women who remained high-risk HPV+ at round 2 had cleared their initial infection and acquired a different HPV type. They had less than 20% of the CIN3+ risk of those with type-specific persistence. Women with HPV 16 or HPV 18 and normal cytology are being referred to immediate colposcopy in some centres in the national pilot. Strategies based on full or partial HPV typing could be considered in triage as well as in primary HPV screening. Future work will focus on the implications of more sensitive HPV testing for primary HPV screening policy and triage of HPV-positive women. Our results suggest that a more sensitive test is needed to detect occult CIN3 at high risk of progression to cancer, but this would substantially increase the overall HPV detection rate. Tests such as DNA methylation for distinguishing HPV infection from neoplasia will be evaluated on stored samples and on further samples now being collected from women in the cohort who are still being screened.

Funding

Chapter 1 Introduction

The NHS Cervical Screening Programme is already one of the most successful in the world in preventing cervical cancer,[1,2] but unnecessary referral and treatment should be minimised to reduce NHS costs, inconvenience to women and unnecessary treatment for low-grade cervical dysplasia, which can compromise later birth outcomes. Human papillomavirus (HPV) testing is already used in the UK to triage borderline and mild cervical cytology and as a test of cure following excision of cervical intraepithelial neoplasia (CIN). National roll-out of primary HPV testing, scheduled to be complete by December 2019, will further increase sensitivity; however, referrals and, hence, costs will also increase without longer screening intervals and more efficient triage methods for human papillomavirus-positive (HPV+) women. Primary HPV testing with cytology triage of HPV+ women is being piloted at several sites in England following publication of ARTISTIC trial (A Randomised Trial In Screening To Improve Cytology) results over three rounds of HPV screening[3–5] and pooled data from ARTISTIC and other randomised trials showing a reduction in long-term cervical cancer risk.[6] The aim of primary HPV screening is to reduce cervical cancer risk by identifying women with high-grade CIN early enough to prevent progression to invasive cancer. The introduction of primary HPV testing in the NHS Cervical Screening Programme will require practical decisions on screening intervals for different age ranges as well as the triage protocol for HPV+ women. The results up to 2009 from the initial screening rounds in ARTISTIC contributed to the decision to pilot HPV primary screening,[7] and this extension to 2015 gave a 10-year follow-up from entry, providing further evidence to optimise screening protocols.

The CIN grade 3 or cervical cancer (CIN3+) rate in the second round of ARTISTIC was less than half the rate at entry, as the majority of cases diagnosed at entry reflected a long-term accumulation missed by previous screening.[5] Virtually all prevalent cases will be detected when HPV screening is first introduced. Therefore, follow-up from round 1 represents what will be seen when primary HPV screening is introduced, while follow-up from round 2 represents what will be seen at the second and subsequent rounds of HPV screening. For the purpose of modelling an established HPV screening programme, an important group are the 85% of women who were human papillomavirus negative (HPV–) at entry (round 1), as long follow-up of those with new infections detected at round 2 represents the time course of HPV persistence and CIN3+ risk following first infection. Extending follow-up to 2015 has increased the median follow-up beyond round 2 in ARTISTIC from 4 to 10 years.

Follow-up of the cohort to 2009 showed that the subsequent CIN3+ rate is substantially lower following a single negative HPV test than for negative cytology,[4] and this was influential in the National Screening Committee's (NSC's) recommendation that HPV testing should replace cytology as the primary screening test. This further follow-up beginning at round 2 will show whether or not the screening interval can safely be increased from the current routine (3 years for those aged < 50 years and 5 years for those aged ≥ 50 years) to up to 10 years for HPV– women, irrespective of previous test results.

Chapter 2 Objectives

The objective of this extended follow-up of the ARTISTIC cohort was to obtain the data required to evaluate the long-term benefits of alternative screening strategies using primary HPV testing, including the following:

1. The long-term cumulative CIN3+ risk following a negative HPV test, and, hence, the safe screening interval at different ages.
2. The effect of HPV type on CIN3+ risk following a positive HPV test, and, hence, the role of HPV genotyping in routine screening.
3. The difference in CIN3+ risks following round 2 between women with type-specific HPV persistence since round 1 and those with a newly acquired HPV type. This is relevant to the triage protocol for HPV+ women: the interval to retesting, and either referral for colposcopic examination or further testing in women who remain HPV+ based on HPV typing and cytology.
4. The effects on CIN3+ risk of different ages at starting and stopping screening. The high prevalence of CIN2+ at age 20–24 years (6.3%) in round 1 of ARTISTIC[4] showed that many cases detected when women are first screened at age 25 years developed more than 5 years earlier. The long-term CIN3 risk in HPV– women who are aged ≥ 50 years is very low, but if they are never screened again their lifetime then cancer risk may not be negligible.

Chapter 3 Methods

Data collection during the trial (2001–9)

ARTISTIC compared cytology with and without HPV testing among 24,510 women attending routine cervical screening in 2001–3. Over 60,000 HPV tests [hybrid capture 2 (HC2) with full HPV typing of those testing positive] were performed on routinely collected liquid-based cytology (LBC) cervical samples until September 2009. Methods are described elsewhere[3,5] reporting that women were randomly allocated in a ratio of 1 : 3 between having their HPV results concealed (concealed arm, $n = 6124$) or revealed (revealed arm, $n = 18,386$). All women with abnormal cytology were recalled for retesting or referred to colposcopy according to national guidelines.[3] After March 2008, the laboratory became part of the Sentinel Sites project in which low-grade cytological abnormalities were triaged using HPV. Women were referred with borderline or mild cytology only if they tested positive for HPV; otherwise, they were returned to routine recall. In addition, women in the revealed arm with normal cytology who were hybrid capture 2 positive (HC2+) were recalled for repeat HPV testing, and those whose HPV infection persisted were referred to colposcopy.

Liquid-based cytology was carried out using ThinPrep® (Hologic, Crawley, UK) and HPV testing using HC2 (Qiagen, Crawley, UK). A cut-off point of 1 relative light unit/mean control (RLU/Co) pg/µl was used to identify positive HPV samples, which were genotyped using at least one of three HPV typing assays. All HC2+ samples during rounds 1 and 2 were genotyped using the prototype Roche Line Blot Assay (Roche Molecular Diagnostics, Pleasanton, CA, USA).[3] This was replaced by the commercially available Linear Array assay and the PapilloCheck® assay (Greiner Bio-one GmbH, Frickenhausen, Germany) during round 3. In addition, approximately two-thirds of archived HC2+ round 1 samples were also tested by the PapilloCheck assay and one-third of archived HC2+ round 2 samples were tested by the Roche Linear Array®. In all three rounds, any of the 13 high-risk human papillomavirus (HRHPV) types detected by HC2 (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) that was detected by any of the assays was included in the analysis. All other HPV types were ignored in all analyses.

After the trial ended in 2009, all women returned to routine cytology every 3 years if they were aged < 50 years, and every 5 years if they were aged 50–64 years. We have published reports on baseline data,[8,9] follow-up through two further screening rounds[3–5,10] and various other HPV-related issues.[6,11–13] These analyses were based on follow-up to 2009 through two cytology laboratories in the Manchester area. Any women moving out of the area were lost, and only 60% of the ARTISTIC cohort had a cytology record between 2006 and 2009.

Further data collection (2010–16)

NHS Central Register for cancer incidence and mortality
The cohort was flagged through NHS Central Register (NHSCR), giving notification of deaths and cancer diagnoses, including carcinoma in situ of the cervix (CIN3), until December 2015.

National screening programme call–recall cytology and human papillomavirus records
The cohort was linked to the NHS Cervical Screening Programme call–recall database to obtain lifetime cervical screening records for the entire ARTISTIC cohort. This included any recorded HPV results taken after triaging of borderline or mild dyskaryosis cytology or as part of primary HPV screening (in pilot areas). The reasons for ceasing screening, including hysterectomy, were also recorded.

Testing stored samples for human papillomavirus deoxyribonucleic acid

All samples taken during the trial have been tested using HC2 with HPV typing for HC2+ samples. Women who consented to their HPV samples being retained for future research are now stored at Professor Lorincz's laboratory at QMUL. Sensitive polymerase chain reaction (PCR)-based assays [Roche Line Blot assay and PapType® assay (Genera Biosystems, Scoresby, VA, Australia)] were carried out on hybrid capture 2-negative (HC2–) samples from women who have developed invasive cervical cancer since 2009.

Chapter 4 Definitions and statistical methods

Definition of round 2 follow-up

In previous reports, round 2 was defined as the first adequate cytology between 26 and 54 months after entry, which included 10% with no adequate HPV test on their round 2 sample. In this report, round 2 is defined as the first adequate HPV test between 30 and 48 months after entry. Under this definition, 13,591 women had a round 2 test, on average, 3 years and 7 months after entry. In analyses beginning at round 2, 185 women with CIN3+ registration/histology before this date and six women whose flagging data indicated that they had cancelled from the NHSCR before this date were excluded.

Human papillomavirus clearance

To estimate and compare clearance rates of recently acquired and long-standing HPV infections (i.e. those already present at entry), clearance from the second HPV test in ARTISTIC (regardless of time since entry) was assessed. Women with any histology, regardless of result, between the second and third HPV tests were excluded in case the action of taking a biopsy affected the clearance rate. In addition, women with CIN3+ histology before the second HPV test were excluded. A total of 1026 women with at least three HPV tests whose second test was positive for HRHPV were included in the analysis. Each infection with a HPV type was considered independently, so women with more than one HPV type were counted more than once in the analysis. Clearance of each infection was calculated by time between the second and third HPV test and stratified by whether or not the same HPV type was present at entry (i.e. whether the infection developed since entry or was prevalent at entry).

Human papillomavirus recurrence

The recurrence of type-specific HPV infections was counted in women who had HRHPV infections at round 1 and subsequently tested HC2–. The time to 'clearance' (defined as testing HC2–) was stratified into 'short term', defined as clearance of < 24 months after round 1, and 'long term', defined as clearance 24–54 months after round 1. Recurrence in these two groups of women was defined as any subsequent HRHPV+ result with one or more genotype identified that was also present at entry. Under the protocol, genotyping was not carried out on HC2– samples, which implies that 'clearance' means that the HPV infection had become undetectable by HC2.

Type-specific human papillomavirus persistence

The HPV types found in round 2 (30–48 months after entry) were compared with those identified in round 1 so that round 2 infections could be classified as new or persistent. Women with a type-specific persistent infection with or without a new infection of a different genotype were classified as persistent.

Human papillomavirus status

In most other analyses, women were classified hierarchically into mutually exclusive groups: HPV 16 or HPV 18, any of HPV types 31, 33, 45, 52 or 58 (without 16 or 18), any other HRHPV, HC2+ with no HRHPV, or HC2–.

Calculation of cumulative risk for cervical intraepithelial neoplasia or cervical cancer

Cumulative CIN3+ risks were estimated by Kaplan–Meier methods. Subgroups were compared using the log-rank test. Cumulative risks were calculated from entry (round 1) and also from round 2 when incident and persistent infections could be distinguished. Women were censored at date of last cytology prior to hysterectomy according to call–recall data. All analyses were censored on 30 April 2015 to allow for late registration of CIN3 and cancer.

Kaplan–Meier analysis of interval-censored data

The aim of the cumulative risk analyses is to estimate the probability that CIN3+ would be detected by a test at a given time after entry to follow-up, beginning either at entry to the trial or at round 2. This raises several issues.

1. We ignore the possibility that CIN3 occasionally regresses, so cumulative risks may overestimate the prevalence that would be observed if the next test were 5 or 10 years later.
2. CIN3+ histology is backdated to the beginning of follow-up if the histology/registration occurred within a year of the beginning of follow-up. These cases are shown at time zero giving an initial step in the Kaplan–Meier curve. Some of these cases were not present at the time of the initial abnormal cytology or positive HPV test but developed during the period of repeat testing.
3. Later CIN3+ histology/registration dates are backdated to the first test in the preceding year, then further backdated to the mid-point of the interval between that test and the preceding test. For three cancers and a single CIN3 lesion with no recorded cytology within a year, the histology date is taken as the end of the interval. One further cancer was censored on ceasing screening and thus excluded.

This modified Kaplan–Meier treatment of interval-censored data, in which lesions are assigned to the mid-point of the screening interval where they became detectable, gives results similar to a parametric analysis (Professor Peter Sasieni, Queen Mary University of London, 2017, personal communication). The second-order error is that the interval mid-point is not the expected value of the time when the CIN3 would be detectable, which may be slightly earlier or later depending on the assumed model of HPV acquisition and CIN3 development.

Chapter 5 Results

Section 1: description of data

Eligible data

The cohort that participated in ARTISTIC consisted of 24,510 women aged between 20 and 64 years and provided an adequate cytology and HPV test at enrolment. Fourteen women did not have a valid NHS number and so 24,496 women were flagged with NHS Digital for cancer registration and death. These women were then linked to the National Screening Programme call–recall system, which yielded a final cohort of 23,888 after excluding three non-matches and 605 type-2 opt-outs (those opting out of their data being accessed for medical research) (*Figure 1*). The call–recall data were linked by NHS number to ensure correct linkage. At least one cytology date and result from the laboratory database matched the call–recall data in all but 53 women (99.8%). These 53 women were individually examined and most had only one or two tests identified through the laboratory. We assumed that these cytology dates had not been recorded correctly on the call–recall system. For those whose call–recall screening records matched the Manchester laboratory data during the trial (2001–9), it was not uncommon for some records to be inconsistent between the systems.

Follow-up via local histology laboratories to 2009 when the trial ended and via cancer registrations to April 2015 identified 509 cases of CIN3+, including 23 invasive cancers. Three cases of CIN3 were excluded owing to censoring at last cytology as no link was made to call–recall data. In addition, one invasive cancer was excluded as the woman's screening record indicated that she had ceased screening after reaching the age of 65 years. Therefore, 505 cases of CIN3+ were included in the analysis (*Table 1*).
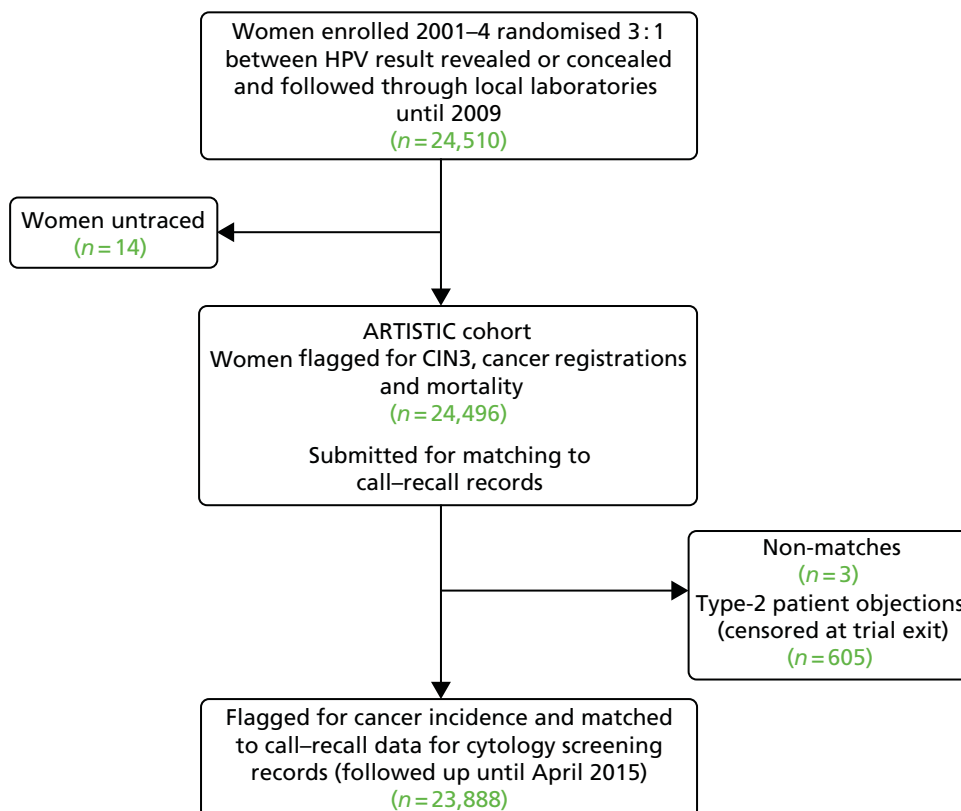
FIGURE 1 The CONSORT (Consolidated Standards of Reporting Trials) flow of diagram showing women followed up for cancer registration and mortality through national registration, and for cytology through call–recall cervical screening records.

TABLE 1 The CIN3 and invasive cancer cases

	Histology only (2001–9), n (%)	Registration only (2001–15), n (%)	Both histology and registration, n (%)	Total number
CIN3	99 (20.4)	94[a] (19.3)	293 (60.3)	486
Invasive cancer		11[b] (47.8)	12 (52.2)	23
Year of diagnosis				
2001–3	61 (21.2)	7 (2.4)	220 (76.4)	288
2004–6	21 (22.8)	11 (12.0)	60 (65.2)	92
2007–9	17 (23.6)	30 (41.7)	25 (34.7)	72
2010–15	0 (0.0)	57 (100.0)	0 (0.0)	57
Total	99 (19.4)	105 (20.6)	305 (59.9)	509

a Three CIN3 were excluded owing to censoring at last cytology (2007, $n = 1$; 2010, $n = 2$).
b One invasive cancer excluded owing to censoring at ceasing screening at age 64 years (after 2010).

Among women who had not ceased screening due to age by 2016 ($n = 17,602$), 642 women aged 30–64 years were recorded as ceased on the call–recall system due to hysterectomy: 0.3% aged 30–39 years, 2.5% aged 40–49 years, 5.3% aged 50–59 years and 6.9% aged 60–64 years.

Natural history of human papillomavirus infection

Table 2 shows the prevalence of HPV infection at rounds 1 and 2 by age. HC2 was the primary assay used and only HC2+ samples were further genotyped. Overall, 4% of samples tested positive by HC2 but no HRHPV was detected. These have been assumed to be HRHPV– in the analysis shown in *Table 3*, which shows prevalence of HRHPV by age at round 2 among women who were HPV– at round 1, and prevalence rates of type-specific persistence and new infection among those who were HPV+ at round 1. The prevalence of new infection falls steeply with age in those women who were HPV– at round 1, from 19.7% at 20–24 years to 1.0% at 55–64 years. In contrast, among women who were HPV+ at round 1, the proportion with persistence at round 2 (17.9%) shows little or no age trend. Round 2 HPV prevalence in women who were HPV– at entry in ARTISTIC and in the POBASCAM (the Netherlands)[14] and NTCC (Italy) trials[14] are shown by age in *Figure 2* and by HPV type in *Figure 3*, in which ARTISTIC data are restricted to the age range of the NTCC trial. The screening interval was 3 years in ARTISTIC and NTCC and 5 years in the POBASCAM trial. *Figure 2* shows remarkably similar HRHPV rates in England, Italy and the Netherlands above the age of 33 years, but higher rates in ARTISTIC for younger women. *Figure 3* shows the data by HPV genotype.

The proportion of HPV infections clearing increased by time interval to testing (*Table 4*). Clearance of new HPV infections (i.e. infections that had developed in the preceding screening interval) was higher than persisting HPV infections (i.e. those that were present at the previous screening round). Clearance of HPV 16 infection was lower than other infections and approximately 40% of new HPV 16 infections were still persisting in women tested over 3 years.

Short-term recurrence was assessed among 405 women who were HRHPV+ at entry and who tested HC2– less than 2 years after entry (*Table 5*). Of these, 27 (6.7%) women had a recurrent infection of the same HPV type present at entry. Long-term recurrence was assessed among 415 women who were HRHPV+ at entry and tested HC2– at least 2 years later. Of these, only five (1.2%) women had a later recurrence or reinfection of the HPV type present at entry.

TABLE 2 Age-specific HRHPV prevalence at round 1 (entry) and round 2 (30–48 months later)

| Age (years) | Prevalence, n (%) | | | | | Total HRHPV+, n (%) |
	HPV 16/18	HPV 31/33/45/52/58	Other HRHPV	No HRHPV detected (HC2+)	HC2–	
Round 1 (entry)						
20–24	408 (15.7)	254 (9.8)	204 (7.9)	167 (6.4)	1560 (60.2)	2593 (33.4)
25–29	264 (10.2)	200 (7.7)	145 (5.6)	106 (4.1)	1874 (72.4)	2589 (23.5)
30–34	190 (5.2)	200 (5.4)	131 (3.6)	164 (4.5)	2998 (81.4)	3683 (14.2)
35–39	103 (2.6)	104 (2.6)	120 (3.1)	150 (3.8)	3462 (87.9)	3939 (8.3)
40–44	58 (1.7)	56 (1.7)	70 (2.1)	128 (3.8)	3069 (90.8)	3381 (5.4)
45–49	26 (1.0)	42 (1.6)	43 (1.6)	110 (4.1)	2496 (91.9)	2717 (4.1)
50–54	25 (1.1)	29 (1.2)	28 (1.2)	90 (3.8)	2210 (92.8)	2382 (3.4)
55–59	19 (1.0)	10 (0.5)	22 (1.1)	67 (3.4)	1853 (94.0)	1971 (2.6)
60–64	11 (0.9)	7 (0.6)	11 (0.9)	47 (3.8)	1165 (93.9)	1241 (2.3)
Total	1104 (4.5)	902 (3.7)	774 (3.2)	1029 (4.2)	20,687 (84.5)	24,496 (11.4)
Round 2 (30–48 months)						
20–24	36 (9.4)	37 (9.6)	22 (5.7)	29 (7.6)	260 (67.7)	384 (24.7)
25–29	73 (8.1)	57 (6.3)	33 (3.7)	69 (7.6)	673 (74.4)	905 (18.0)
30–34	66 (4.7)	45 (3.2)	30 (2.2)	65 (4.7)	1187 (85.2)	1393 (10.1)
35–39	25 (1.3)	51 (2.5)	40 (2.0)	73 (3.6)	1819 (90.6)	2008 (5.8)
40–44	14 (0.6)	39 (1.7)	19 (0.8)	72 (3.2)	2129 (93.7)	2273 (3.2)
45–49	19 (1.0)	23 (1.2)	11 (0.6)	48 (2.5)	1846 (94.8)	1947 (2.7)
50–54	8 (0.5)	14 (0.8)	13 (0.8)	48 (2.9)	1574 (95.0)	1657 (2.1)
55–59	9 (0.6)	6 (0.4)	8 (0.5)	32 (2.1)	1464 (96.4)	1519 (1.5)
60–64	6 (0.6)	5 (0.5)	7 (0.6)	29 (2.6)	1053 (95.7)	1100 (1.6)
65–69	0 (0.0)	0 (0.0)	3 (0.7)	8 (2.0)	394 (97.3)	405 (0.7)
Total	256 (1.9)	277 (2.0)	186 (1.4)	473 (3.5)	12,399 (91.2)	13,591 (5.3)

Comparison with data from the UK primary human papillomavirus screening pilot

A UK pilot study is trialling primary HPV screening in six sites in England. Women who are HPV+ and have borderline or worse cytology are referred to colposcopy and those with negative cytology are recalled after 12 months for repeat HPV testing and cytology.[15] An immediate effect of introducing primary HPV testing is diagnosis of prevalent CIN3+ which had been missed by previous cytology. This was seen in ARTISTIC,[10] the NTCC trial[16] and in a German study,[17] and a much lower CIN3 rate than at entry will presumably be seen in later screening rounds in the UK pilot study.[15] *Table 6* shows that the prevalence of moderate/ severe cytology among HPV+ women in ARTISTIC was similar at each age in round 1 of ARTISTIC and in the pilot study, but in round 2 it was about three times lower and referral rates were halved. This reflects prevalent disease that had been missed by previous cytology but was reliably detected by HPV testing. When primary HPV testing has been rolled out nationally it may be safe to introduce a longer recall interval for HPV+ women with borderline/mild cytology in round 2 whose previous HPV test was negative.

TABLE 3 Women who were HRHPV+ at round 2 by age at round 2. Results are shown separately for those HRHPV– at entry and those HRHPV+ at entry

| Age (years) at round 2 | Infection status at entry | | | | |
| | HRHPV– | | HRHPV+ | | |
	Number of women	New HRHPV at round 2, *n* (%)	Number of women	New HRHPV at round 2, *n* (%)	Persisting HRHPV type at round 2, *n* (%)
20–24	239	47 (19.7)	145	20 (13.8)	28 (19.3)
25–29	648	77 (11.9)	257	37 (14.4)	49 (19.1)
30–34	1119	60 (5.4)	274	21 (7.7)	60 (21.9)
35–39	1814	68 (3.8)	194	16 (8.2)	32 (16.5)
40–44	2138	48 (2.3)	135	7 (5.2)	17 (12.6)
45–49	1869	37 (2.0)	78	8 (10.3)	8 (10.3)
50–54	1602	24 (1.5)	55	0 (0.0)	11 (20.0)
55–59	1482	14 (0.9)	37	3 (8.1)	6 (16.2)
60–64	1079	12 (1.1)	21	3 (14.3)	3 (14.3)
65–69	396	1 (0.3)	9	0 (0)	2 (22.2)
All women	12,386	388 (3.1)	1205	115 (9.5)	216 (17.9)

Persistence indicates the same HRHPV type at both rounds.
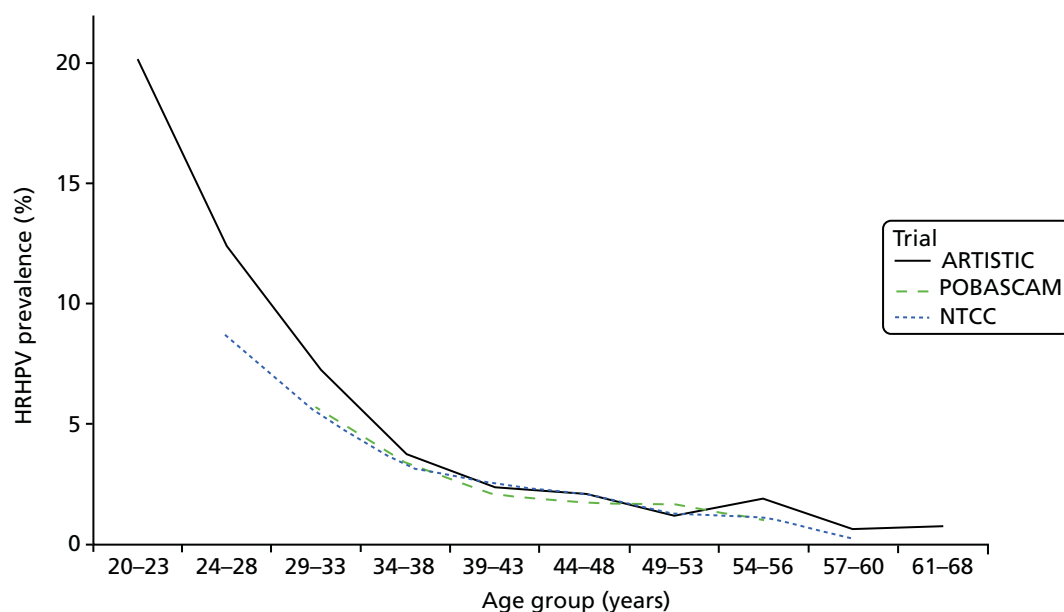
FIGURE 2 New infections: prevalence of HRHPV at round 2 in the ARTISTIC, NTCC (Italy) and POBASCAM (the Netherlands) trials in women who were HRHPV– at entry.
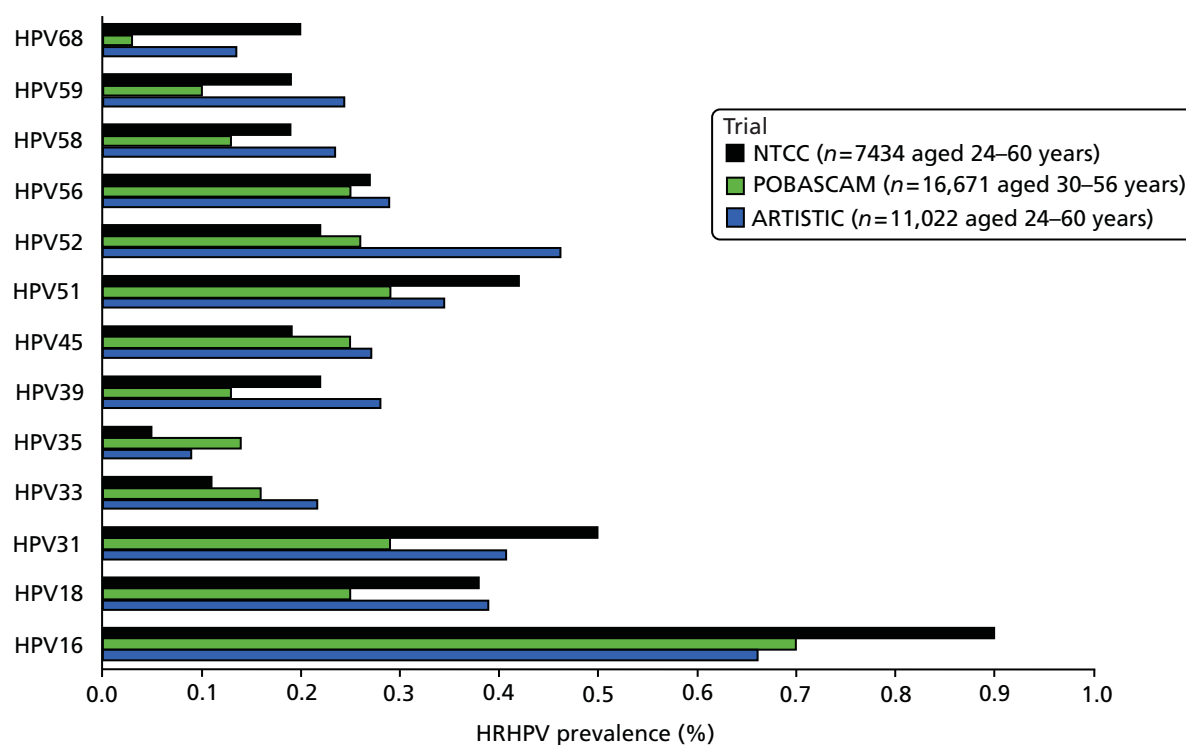
FIGURE 3 New infections: prevalence (%) at round 2 of each HRHPV type in the ARTISTIC, NTCC and POBASCAM trials in women who were HRHPV– at entry.

TABLE 4 Clearance of new and persistent HRHPV infections

Infections	Proportion of infections clearing by time to next HPV test, n/N (%)			
	< 1 year	1–2 years	2–3 years	≥ 3 years
New HPV 16 infections	20/51 (39.2)	18/26 (69.2)	7/13 (53.9)	7/12 (58.3)
Other new infections	142/249 (57.0)	107/144 (74.3)	53/65 (81.5)	66/74 (89.2)
All new infections[a]	162/300 (54.0)	125/170 (73.5)	60/78 (76.9)	73/86 (84.9)
HPV 16: present at entry	20/94 (21.3)	12/22 (54.6)	9/21 (42.9)	7/12 (58.3)
Other infections: present at entry	91/243 (37.5)	52/104 (50.0)	44/65 (67.7)	36/48 (75.0)
All infections present at entry[b]	111/337 (32.9)	64/126 (50.8)	53/86 (61.6)	43/60 (71.7)

a Next HPV test following first detection of 634 HRHPV types in 504 women who did not have that HRHPV type at entry.
b Second HPV test for 609 HRHPV types detected at entry in 522 women.

Invasive cervical cancer

Table 7 shows the 23 invasive cancers identified within the cohort between 2001 and 2015 by HPV result and cytology at entry. The six HC2– samples were further tested using PCR-based assays and five were found to contain HRHPV deoxyribonucleic acid (DNA) (HPV 16 in four women, HPV 51 in one woman). Low levels of HPV 52 DNA were detected in a later sample (3 years after entry but 3 years before cancer registration) taken from the sixth woman. The 10 prevalent cancers diagnosed within 7 months of entry were all PCR+ with moderate or worse cytology, and nine were HC2+. Test positivity at entry for the remaining 13 women whose cancers were diagnosed between 4 and 13 years later was 15% (2/13)

TABLE 5 The HPV type-specific recurrence following a negative HC2 test of HPV infections that were detected at entry

Recurrence	Months from HC2− test to next HPV test					
	0	6	12	24	36	≥ 48
Short-term recurrence (following a HC2− test < 24 months after entry)						
Number of women	26	81	122	118	29	29
Cumulative number of women	26	107	229	347	376	405
Cumulative recurrent infections (%)	2 (7.69)	7 (6.54)	14 (6.11)	21 (6.05)	22 (5.85)	27 (6.67)
Long-term recurrence (following a HC2− test 24–54 months after entry)						
Number of women	11	54	81	77	175	17
Cumulative number of women	11	65	146	223	398	415
Cumulative recurrent infections (%)	0 (0.0)	0 (0.0)	1 (0.68)	1 (0.45)	5 (1.26)	5 (1.20)

TABLE 6 Cytology triage of HPV+ women in the UK primary HPV screening pilot sites and ARTISTIC rounds 1 and 2 by age

Age (years) at test	HPV+,[a] n (%)	Cytology result among HPV+ women, n (%)			Referral rate,[b] %
		Negative	Borderline/mild	Moderate+	
Pilot sites					
25–29	8231 (28.3)	5108 (62.1)	2019 (24.5)	1104 (13.4)	11.0
30–39	6127 (13.6)	4170 (68.1)	1330 (21.7)	627 (10.2)	4.5
40–49	4024 (8.0)	2951 (73.3)	822 (20.4)	251 (6.2)	2.2
50–59	1937 (6.0)	1453 (75.0)	365 (18.8)	119 (6.1)	1.5
60–64	333 (4.7)	273 (82.0)	42 (12.6)	18 (5.4)	0.9
All women	20,652 (12.6)	13,955 (67.6)	4578 (22.2)	2119 (10.3)	4.2
Round 1 ARTISTIC					
25–29	716 (27.7)	374 (52.2)	245 (34.4)	96 (13.4)	13.2
30–39	1161 (15.2)	679 (58.5)	339 (29.1)	144 (12.4)	6.3
40–49	533 (8.7)	343 (64.4)	137 (25.7)	53 (9.9)	3.1
50–59	290 (6.7)	238 (82.1)	40 (13.8)	12 (4.1)	1.2
60–64	76 (6.1)	68 (89.5)	3 (3.9)	5 (6.6)	0.6
All women	2776 (12.7)	1702 (61.3)	764 (27.5)	310 (11.2)	4.9
Round 2 ARTISTIC					
25–29	230 (25.6)	160 (69.6)	63 (27.4)	7 (3.0)	7.8
30–39	393 (11.6)	267 (67.9)	107 (27.2)	19 (4.8)	3.7
40–49	239 (5.7)	193 (80.8)	40 (16.7)	6 (2.5)	1.1
50–59	137 (4.3)	113 (82.5)	23 (16.8)	1 (0.7)	0.8
60–64	46 (4.2)	43 (93.5)	3 (6.5)	0 (0.0)	0.3
All women	1045 (8.2)	776 (74.3)	236 (22.6)	33 (3.2)	2.1

a HC2 assay used in ARTISTIC and either Gen-Probe Aptima® (Gen-Probe Incorp., San Diego, CA, USA), Abbott Realtime® (Abbott Molecular, Maiden head, UK) or Roche COBAS® (Roche Molecular Diagnostics, Pleasanton, CA, USA) assays used in the pilot sites.
b Women who are HPV+ and have abnormal cytology are immediately referred to colposcopy according to the pilot sites protocol.

TABLE 7 Invasive cervical cancers identified through national registration data in 24,946 women by HPV and cytology status at entry (follow-up to 2015)

| Time from entry to cancer registration | Cytology | | HC2+ | | HC2− | | |
	Normal *n* (%)	Abnormal *n* (%)	PCR+ *n* (%)	PCR− *n* (%)	PCR+ *n* (%)	PCR− *n* (%)	Total
0–7 months	0	10 (0.3)	9[a] (0.3)	0	1 (0.6)	0	10
8–47 months	0	0	0	0	0	0	0
4–13 years	11 (0.05)	2 (0.06)	8 (0.3)	0	4 (2.5)	1[b] (0.005)	13
Number of women	21,369	3127	2780	1029	157[c]	20,530	24,496

a The entry sample was HC2+ with glandular neoplasia but insufficient for further testing in a woman whose cancer was diagnosed 4 months after entry. As the remaining 16 HC2+ samples were all PCR+ she is shown as PCR+.
b Low-level HPV52 DNA was detected in a later HC2− sample taken 3 years after entry and 3 years before cancer registration from the only HC2–PCR− woman.
c Estimated from PapilloCheck results at round 3 (0.76% HPV+ in 4473 HC2− samples).[13] Entry samples for women who developed cancer were tested later with RLB, but PCR was not done on other HC2− entry samples.

for cytology, 62% (8/13) for HC2 and 92% (12/13) for PCR. *Table 8* shows that cancer is almost as common as CIN3 in those women aged ≥ 55 years, indicating the need to focus on sensitivity for cancer as well as CIN3 detection in a woman's final (exit) screen. With up to 14 years of follow-up since trial entry in 2001–3, there have so far been no cervical cancer deaths in the cohort.

Section 2: the long-term protection of a negative human papillomavirus test and, hence, the safe screening interval at different ages

Table 9 shows cumulative CIN3+ risks in women testing HC2− at rounds 1 and 2 by age. The 10-year risks decrease from 1.10% [95% confidence interval (CI) 0.69% to 1.77%] in women aged 20 –25 years at entry to 0.08% (95% CI 0.03% to 0.20%) in women aged ≥ 50 years at entry. The 10-year CIN3+ risk in all HPV− women aged 25–39 years was 0.40% (95% CI 0.28% to 0.56%) and significantly higher than the risk in women aged ≥ 40 years at entry (0.11%, 95% CI 0.06% to 0.20%; $p < 0.0001$). *Table 10* shows cumulative risks from round 2 in those HC2− at both time points compared with those women who had cleared an infection present at entry. Risks were based on very small numbers, but were approximately

TABLE 8 National registrations of cervical cancer and CIN3 in ARTISTIC in 2001–15 and in England in 2014

| | Age at registration (years) | | | | |
	20–29	30–39	40–49	50–59	60–69
ARTISTIC					
Cervical cancer	0	7	10	4	2
CIN3	158	163	55	10	2
CIN3-to-cancer ratio	∞	23.3	5.5	2.5	1.0
England					
Cervical cancer	483	643	521	330	230
CIN3	14,458	7752	2692	848	206
CIN3-to-cancer ratio	29.9	12.1	5.2	2.6	0.9

TABLE 9 Cumulative CIN3+ risks following a single HC2– HPV test at round 1 ($n = 20,687$) and at round 2 ($n = 12,399$) by age at test

Women who were HC2– at round 1								
			Risk from round 1					
			2.5-year		**5-year**		**10-year**	
Age (years) at round 1	**Number (%) of women at baseline**	**Number of CIN3+ women[a]**	**Number of CIN3+ women (%)**	**95% CI**	**Number of CIN3+ women (%)**	**95% CI**	**Number of CIN3+ women (%)**	**95% CI**
20–24	1563	19	3	0.19 (0.06 to 0.59)	6	0.39 (0.17 to 0.86)	17	1.10 (0.69 to 1.77)
25–29	1870	16	5	0.27 (0.11 to 0.64)	8	0.43 (0.22 to 0.86)	14	0.76 (0.45 to 1.28)
30–39	6466	20	7	0.11 (0.05 to 0.23)	12	0.19 (0.11 to 0.33)	19	0.30 (0.19 to 0.46)
40–49	5562	9	4	0.07 (0.03 to 0.19)	7	0.13 (0.06 to 0.26)	8	0.14 (0.07 to 0.29)
50–64	5226	4	2	0.04 (0.01 to 0.15)	4	0.08 (0.03 to 0.20)	4	0.08 (0.03 to 0.20)
All women (HC2–)	20,687 (84.5)	68	21	0.10 (0.07 to 0.16)	37	0.18 (0.13 to 0.25)	62	0.31 (0.24 to 0.39)

Women who were HC2– at round 2								
			Risk from round 1					
			2.5-year		**5-year**		**10-year**	
Age (years) at round 2	**Number (%) of women at round 2**	**Number of CIN3+ women**	**Number of CIN3+ women (%)**	**95% CI**	**Number of CIN3+ women (%)**	**95% CI**	**Number of CIN3+ women (%)**	**95% CI**
23–24	304	1	0		1	0.33 (0.05 to 2.35)	1	0.33 (0.05 to 2.35)
25–29	701	0	0		0		0	
30–39	3131	9	4	0.13 (0.05 to 0.34)	5	0.16 (0.07 to 0.38)	9	0.29 (0.15 to 0.56)
40–49	3949	2	1	0.03 (0.00 to 0.18)	1	0.03 (0.00 to 0.18)	2	0.05 (0.01 to 0.20)
50–68	4314	1	1	0.02 (0.00 to 0.16)	1	0.02 (0.00 to 0.16)	1	0.02 (0.00 to 0.16)
All women (HC2–)	12,399 (91.2)	13	6	0.05 (0.02 to 0.11)	8	0.07 (0.03 to 0.13)	13	0.11 (0.06 to 0.2)

TABLE 9 Cumulative CIN3+ risks following a single HC2– HPV test at round 1 (*n* = 20,687) and at round 2 (*n* = 12,399) by age at test (*continued*)

Women who were cytology negative at round 1 (concealed arm only)								
			Risk from round 1					
			2.5-year		5-year		10-year	
Age (years) at round 1	Number (%) of women at baseline	Number of CIN3+ women[a]	Number of CIN3+ women (%)	95% CI	Number of CIN3+ women (%)	95% CI	Number of CIN3+ women (%)	95% CI
20–24	489	11	4	0.82 (0.31 to 2.17)	9	1.85 (0.97 to 3.53)	11	2.27 (1.26 to 4.06)
25–29	523	9	2	0.38 (0.10 to 1.52)	4	0.77 (0.29 to 2.03)	8	1.55 (0.78 to 3.08)
30–39	1642	13	6	0.37 (0.16 to 0.81)	8	0.49 (0.25 to 0.98)	11	0.68 (0.37 to 1.22)
40–49	1340	3	0		1	0.07 (0.01 to 0.53)	2	0.15 (0.04 to 0.60)
50–64	1341	2	1	0.07 (0.01 to 0.53)	2	0.15 (0.04 to 0.60)	2	0.15 (0.04 to 0.60)
All women (cytology negative)	5335	38	13	0.24 (0.14 to 0.42)	24	0.45 (0.30 to 0.67)	34	0.65 (0.46 to 0.90)

a In 12 years of follow-up.

three times higher among those women who cleared an infection at entry. Presumably this is confounded with sexual activity and, hence, risk of acquiring a new HPV infection. *Figure 4* and the bottom panel of *Table 9* show a similar CIN3+ risk 10 years after a negative HPV test (0.31%, 95% CI 0.18% to 0.49% in the revealed arm) and 3 years after a negative cytology test (0.30%, 95% CI 0.23% to 0.41% in the concealed arm). These data support a much longer screening interval after a negative HPV test than after a negative cytology test.

Section 3: the role of human papillomavirus typing

The increasing availability of partial genotyping allows risk-based stratification in an organised screening programme. Four of the six sites are utilising partial typing HPV tests (Roche COBAS and Abbott Realtime assays) in the English pilot study, which both allow identification of HPV 16 and HPV 18 infections. *Table 11* and *Figure 5* show that the cumulative risk for women with HPV 16 is much higher than for any other genotype. Women with HPV 16 constituted 22% of all HC2+ infections, but 57% of CIN3+ occurred among this group of women, giving a 10-year cumulative CIN3+ risk of 29.8% (95% CI 26.8% to 33.0%). HPV 18 was a much less common type among ARTISTIC women, constituting 9% of all HC2+ infections (including 2% who also had HPV 16) and the 10-year cumulative risk did not differ from the group of types including 31, 33, 45, 52 and 58. It is clear that assays that could identify these five types in addition to HPV 16 and 18 would be beneficial for a risk-based referral strategy.

Table 12 and *Figure 6* show the risks following two tests approximately 3 years apart. The 10-year cumulative CIN3+ risk following a new HPV infection is low at 3.4% (95% CI 2.1% to 5.4%). The 10-year CIN3 risk from round 2 was no higher in those women who were HPV+ with another type at round 1 (2.7%, 95% CI 0.9% to 8.0%) than in those women who were HPV– at round 1 (3.6%, 95% CI 2.2% to 6.0%).

The highest risks were associated with type-specific persistent infections that, overall, conferred a 10-year cumulative risk of 20.4% (95% CI 15.65% to 26.45%). HPV 16 again showed the highest risks and the 10-year risk following a new infection reached 7.3% (95% CI 3.7% to 14.1%), suggesting that any women with HPV 16 detected could be referred immediately. Of the 331 women with double-positive HRHPV tests
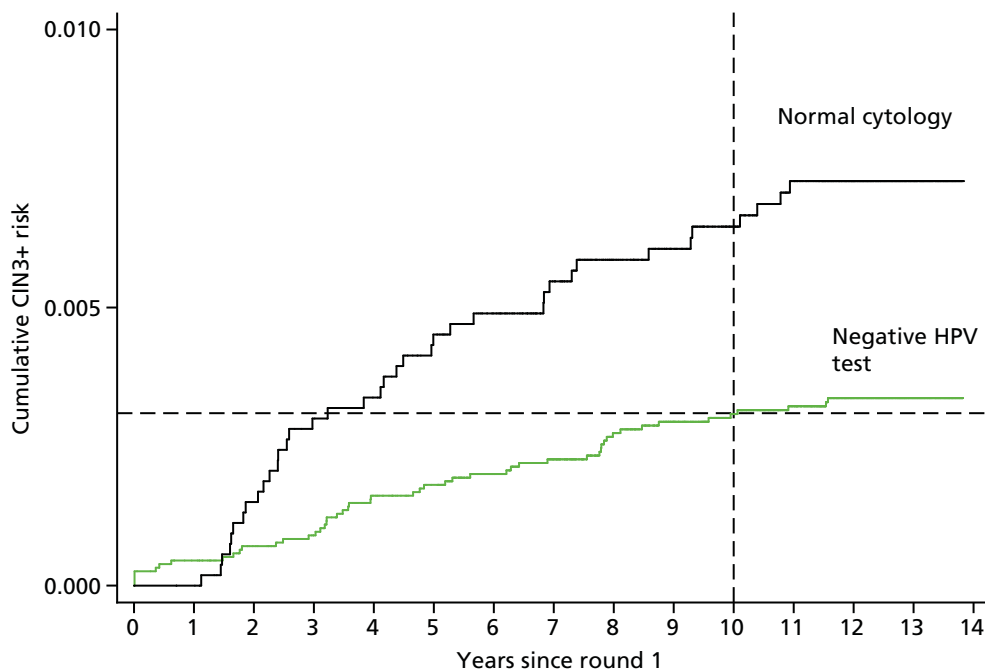
FIGURE 4 Cumulative CIN3+ risk (%) following a negative HPV test or normal cytology at entry.

TABLE 10 Cumulative CIN3+ risks by combination of results at round 1 and at round 2 (30–48 months after round 1)

| HPV status at rounds 1 and 2 | Number of women at round 2 | Number of CIN3+ women | Risk from round 2 | | | | | |
| | | | 2.5-year | | 5-year | | 10-year | |
			Number of CIN3+ women (%)	95% CI	Number of CIN3+ women (%)	95% CI	Number of CIN3+ women (%)	95% CI
HC2 results (aged 20–64 years at entry)								
HC2 double positive	510	54	45	8.8 (6.7 to 11.6)	49	9.6 (7.4 to 12.5)	54	10.6 (8.2 to 13.6)
HC2 negative positive	682	15	12	1.8 (1.0 to 3.1)	14	2.1 (1.2 to 3.5)	15	2.2 (1.3 to 3.6)
HC2 positive negative	1249	3	1	0.08 (0.01 to 0.57)	2	0.16 (0.04 to 0.65)	3	0.25 (0.08 to 0.76)
HC2 double negative	11,150	10	5	0.04 (0.02 to 0.11)	6	0.05 (0.02 to 0.112)	10	0.09 (0.05 to 0.17)
Aged 25–39 years at entry								
HC2 positive negative	615	3	1	0.16 (0.02 to 1.15)	2	0.33 (0.08 to 1.30)	3	0.49 (0.16 to 1.52)
HC2 double negative	4019	6	3	0.07 (0.02 to 0.23)	3	0.07 (0.02 to 0.23)	6	0.15 (0.07 to 0.33)
Aged 40–64 years at entry								
HC2 positive negative	410	0	0		0		0	
HC2 double negative	6673	3	2	0.03 (0.01 to 0.12)	2	0.03 (0.01 to 0.12)	3	0.05 (0.02 to 0.15)

TABLE 11 Cumulative CIN3+ risks following a single HPV test at entry by HPV genotype

Single HPV test at round 1	Number (%) of women at baseline	Number of CIN3+ women[a]	Risk from round 1					
			2.5-year		5-year		10-year	
			Number of CIN3+ women (%)	95% CI	Number of CIN3+ women (%)	95% CI	Number of CIN3+ women (%)	95% CI
HPV 16	831 (3.4)	249	219	26.4 (23.5 to 29.5)	238	28.7 (25.7 to 31.9)	247	29.8 (26.8 to 33.0)
HPV 18	273 (1.1)	36	23	8.4 (5.7 to 12.4)	32	11.7 (8.4 to 16.2)	36	13.2 (9.7 to 17.9)
HPV 31/33/45/ 52/58	902 (3.7)	104	75	8.3 (6.7 to 10.3)	89	9.9 (8.1 to 12.0)	101	11.3 (9.4 to 13.5)
Other HRHPV	774 (3.2)	30	20	2.6 (1.7 to 4.0)	26	3.4 (2.3 to 4.9)	29	3.8 (2.6 to 5.4)
HC2+ non-high risk[b]	1029 (4.2)	18	8	0.8 (0.4 to 1.6)	13	1.3 (0.7 to 2.2)	18	1.8 (1.1 to 2.8)
All HC2+	3809 (15.5)	437	345	9.1 (8.2 to 10.0)	398	10.5 (9.5 to 11.5)	431	11.4 (10.4 to 12.4)
HC2–	20,687 (84.5)	68	21	0.10 (0.07 to 0.16)	37	0.18 (0.13 to 0.25)	62	0.31 (0.24 to 0.39)
Total women	24,496 (100)	505	366		435		493	

a In 12 years of follow-up.
b HC2+ but no HRHPV detected, including 27 women at entry with insufficient samples for typing (in whom two CIN3+ cases were diagnosed).
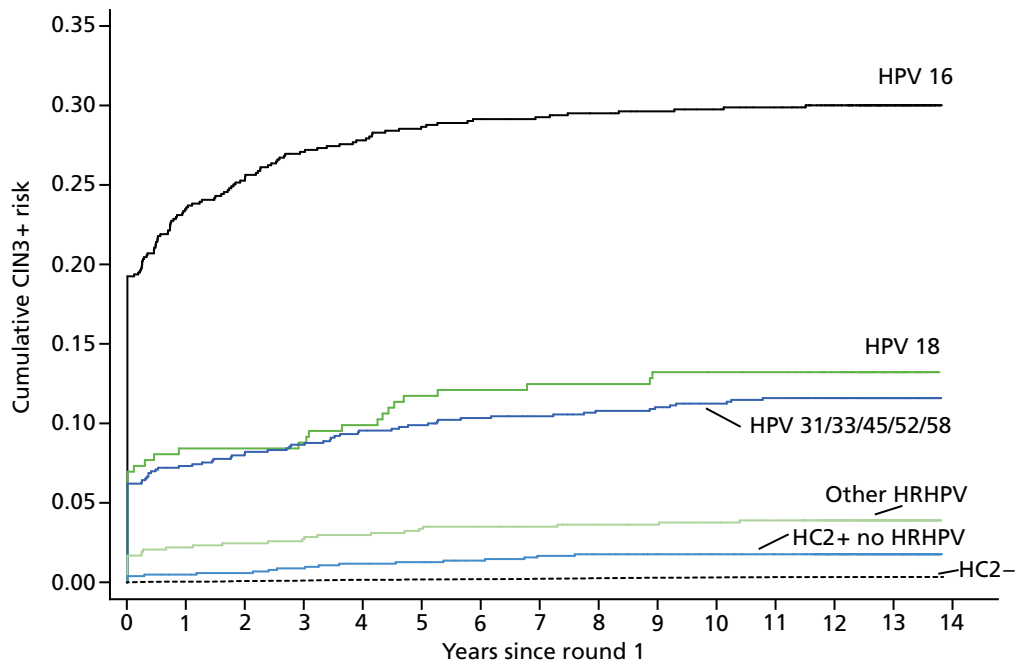
FIGURE 5 Cumulative CIN3+ risks by HPV detection from entry (483 CIN3, 23 invasive cervical cancers in 24,500 women).

(see *Table 3*), 115 (35%) were positive with a new HPV type at the second test and 216 (65%) was type-specific persistent. The proportion of new infections was highest in younger women (43% in women in their 20s) and decreased to just 23% of double-positive infections in women aged ≥ 50 years.

Section 4: triage of human papillomavirus-positive women, particularly the interval to retesting for human papillomavirus-positive women

Table 13 shows cumulative CIN3+ risks by HPV type and cytology at entry. Referring moderate or worse cytology to immediate colposcopy is clearly a highly effective strategy for identifying those women at highest risk of disease (52% by 5 years). Among HC2+ women, the 10-year cumulative CIN3+ risks in those with negative and borderline/mild cytology were estimated to be 4.1% (95% CI 3.3% to 5.0%) and 10.3% (95% CI 8.7% to 12.2%), respectively. These risks vary by HPV genotype, and, hence, a partial genotyping assay could identify those at highest risk (e.g. HPV 16 or 18). *Table 14* is restricted to the 1116 women who were HC2+ and cytology negative and had a follow-up sample taken 30–48 months later (round 2). The current UK protocol for HC2+ cytology-negative women is to repeat HPV and cytology testing at 12 and 24 months and refer all those still HPV+ at 24 months. *Table 14* shows these women under a protocol of repeat testing after a 3-year recall interval. This excludes 10 CIN3+ that were diagnosed in cytology-negative HPV+ women in the revealed arm who were diagnosed before the round 2 test, but under a 3-year recall protocol would probably have been diagnosed at round 2. Analysis restricted to the concealed arm would avoid this bias. Only 277 out of the 1120 women in *Table 14* were in the concealed arm and the results were consistent between the arms; therefore, they were pooled to maximise numbers. The majority of women cleared their infection by round 2, with 72% testing HC2− and a further 7% who remained HC2+ in whom no HRHPV was detected. A small proportion (1.3%) of women developed moderate or worse cytology by round 2, most (9 out of 15) of whom had CIN3+ immediately diagnosed. Out of 220 women who remained HPV+ with normal, borderline or mild cytology, 38% were infected with a new HPV type and 62% were type-specific persistent. Among the new infections, the 10-year cumulative CIN3+ risk remained low (3.7%, 95% CI 1.2% to 11.0%). The risks were slightly higher for those women with borderline or mild cytology, but there was insufficient power to detect a significant difference. Further genotyping of these samples to determine type-specific persistence would refer only those women at highest risk of developing CIN3+ to colposcopy.

TABLE 12 Cumulative CIN3+ risks following round 2 for women with and without type-specific persistence of HPV infection since round 1

HPV status at round 2	Number of women at round 2	n CIN3+	Risk from round 2						
			2.5-year		5-year		10-year	
			n CIN3+ (%)	95% CI	n CIN3+ (%)	95% CI	n CIN3+ (%)	95% CI
Women with type-specific persistence								
Persistent HPV 16	66	22	20	30.3 (20.7 to 42.9)	21	31.8 (22.1 to 44.5)	22	33.4 (23.4 to 46.1)
Persistent HPV 18	23	3	3	13.0 (4.4 to 35.2)	3	13.0 (4.4 to 35.2)	3	13.0 (4.4 to 35.2)
Persistent 31/33/45/52/58	83	15	12	14.5 (8.5 to 24.1)	13	15.7 (9.4 to 25.4)	15	18.1 (11.3 to 28.2)
Persistent other HRHPV	44	4	3	6.8 (2.3 to 19.7)	4	9.1 (3.5 to 22.4)	4	9.1 (3.5 to 22.4)
Any HRHPV type specific persistence	216	44	38	17.6 (13.1 to 23.4)	41	19.0 (14.4 to 24.9)	44	20.4 (15.6 to 26.4)
Women without type-specific persistence								
New HPV 16	109	8	7	6.4 (3.1 to 13.0)	8	7.3 (3.7 to 14.1)	8	7.3 (3.7 to 14.1)
New HPV 18	50	0	0	0.0	0	0.0	0	0.0
New 31/33/45/52/58	193	8	7	3.6 (1.8 to 7.5)	7	3.6 (1.8 to 7.5)	8	4.2 (2.1 to 8.1)
New other HRHPV	151	1	0	0.0	0	0.0	1	0.7 (0.1 to 4.8)
Any new HRHPV	503[a]	17	14	2.8 (1.7 to 4.7)	15	3.0 (1.8 to 4.9)	17	3.4 (2.1 to 5.4)
HC2+ but no HRHPV	473	8	5	1.1 (0.4 to 2.5)	7	1.5 (0.7 to 3.1)	8	1.7 (0.9 to 3.4)
HC2–	12,399	13	6	0.05 (0.02 to 0.11)	8	0.07 (0.03 to 0.13)	13	0.11 (0.06 to 0.19)
HC2 results ignoring genotyping								
HC2 double positive	510	54	45	8.8 (6.7 to 11.6)	49	9.6 (7.4 to 12.5)	54	10.6 (8.2 to 13.6)
HC2 negative positive	682	15	12	1.8 (1.0 to 3.1)	14	2.1 (1.2 to 3.5)	15	2.2 (1.3 to 3.6)
HC2 positive negative	1249	3	1	0.08 (0.01 to 0.57)	2	0.16 (0.04 to 0.65)	3	0.25 (0.08 to 0.76)
HC2 double negative	11,150	10	5	0.04 (0.02 to 0.11)	6	0.05 (0.02 to 0.112)	10	0.09 (0.05 to 0.17)
All women	13,591	82	63		71		82	

a 115 (23%) HRHPV+ at round 1.
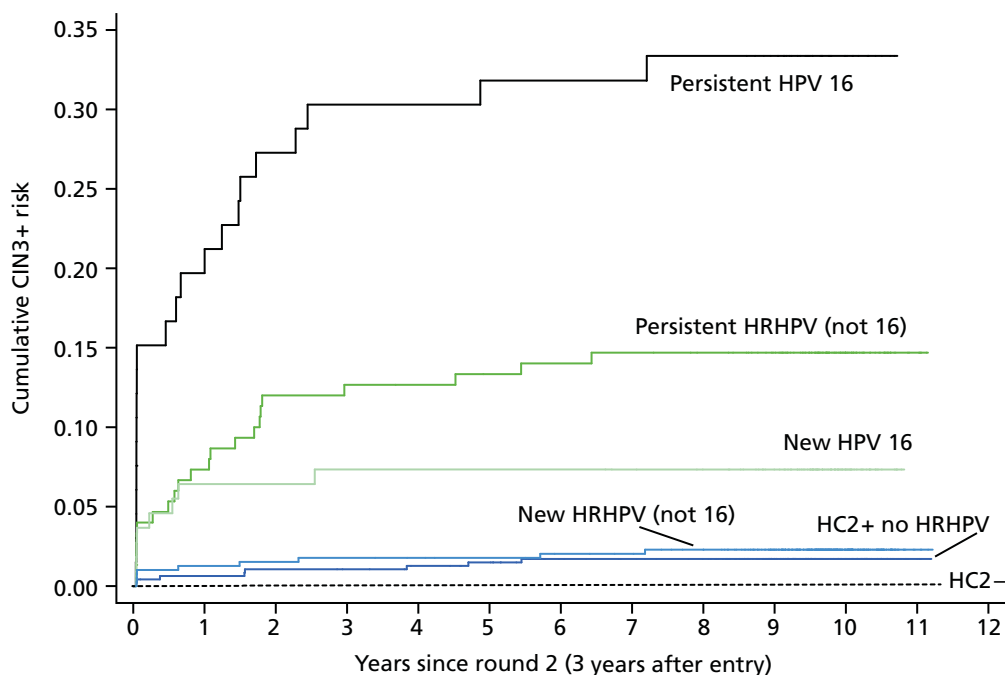
FIGURE 6 Cumulative CIN3+ risks following round 2 for persistent and newly acquired HPV infection (82 CIN3+ in 13,591 women).

Tables 15 and *16* show cumulative CIN3+ risks following new and persisting HPV infections at round 2 in women with negative and borderline/mild cytology, respectively. Similar patterns are seen, with the highest risks in women with persisting infections and in those with HPV 16 infections.

Section 5: optimal ages at starting and stopping screening

Table 17 and *Figure 7* show that the cumulative CIN3+ risk 5 years after round 2 in women with type-specific persisting infection is similar regardless of age before the age of 40 years (23.8%, 95% CI 18.2% to 30.9%), but significantly lower in women aged ≥ 40 years (6.8%, 95% CI 2.3% to 19.7%; $p = 0.02$). Persistent HPV 16 infections account for 44% of the type-specific infections in those women aged < 30 years, but only 11% among women aged ≥ 40 years.

TABLE 13 Cumulative CIN3+ risks following a single HPV test at round 1 by HPV type and cytology

Negative cytology at round 1	Number (%) of women at baseline	Number of CIN3+ women[a]	Risk from round 1					
			2.5-year		5-year		10-year	
			Number of CIN3+ women (%)	95% CI	Number of CIN3+ women (%)	95% CI	Number of CIN3+ women (%)	95% CI
HPV 16	332 (1.6)	41	22	6.6 (4.4 to 9.9)	36	10.9 (8.0 to 14.7)	41	12.4 (9.3 to 16.5)
HPV 18	146 (0.7)	10	1	0.7 (0.1 to 4.8)	6	4.1 (1.9 to 8.9)	10	6.9 (3.8 to 12.4)
HPV 31/33/45/52/58	482 (2.3)	25	6	1.3 (0.6 to 2.8)	14	2.9 (1.7 to 4.9)	22	4.6 (3.1 to 7.0)
Other HRHPV	479 (2.2)	9	3	0.6 (0.2 to 1.9)	7	1.5 (0.7 to 3.1)	8	1.7 (0.8 to 3.3)
HC2+ non-high risk[b]	784 (3.7)	9	1	0.1 (0.02 to 0.90)	5	0.6 (0.3 to 1.5)	9	1.2 (0.6 to 2.2)
All HC2+	2223 (10.4)	94	33	1.5 (1.1 to 2.1)	68	3.1 (2.4 to 3.9)	90	4.1 (3.3 to 5.0)
HC2−	19,146 (89.6)	53	11	0.06 (0.03 to 0.10)	25	0.13 (0.09 to 0.19)	48	0.26 (0.19 to 0.34)
All women with negative cytology	21,369 (100)	147	44		93		138	

Borderline/mild cytology at round 1	Number (%) of women at baseline	Number of CIN3+ women[a]	Risk from round 1					
			2.5-year		5-year		10-year	
			Number of CIN3+ women (%)	95% CI	Number of CIN3+ women (%)	95% CI	Number of CIN3+ women (%)	95% CI
HPV 16	283 (10.6)	65	54	19.1 (15.0 to 24.0)	59	20.9 (16.6 to 26.1)	63	22.3 (17.9 to 27.6)
HPV 18	93 (3.5)	10	7	7.5 (3.7 to 15.1)	10	10.8 (5.9 to 19.1)	10	10.8 (6.0 to 19.1)
HPV 31/33/45/52/58	309 (11.6)	31	24	7.8 (5.3 to 11.4)	29	9.4 (6.6 to 13.2)	31	10.1 (7.2 to 14.0)
Other HRHPV	259 (9.7)	10	7	2.7 (1.3 to 5.6)	9	3.5 (1.8 to 6.6)	10	3.9 (2.1 to 7.1)
HC2+ non-high risk[b]	226 (8.5)	6	4	1.8 (0.7 to 4.7)	5	2.2 (0.1 to 5.2)	6	2.7 (1.2 to 5.8)
All HC2+	1170 (43.9)	122	96	8.2 (6.8 to 9.9)	112	9.6 (8.0 to 11.4)	120	10.3 (8.7 to 12.2)
HC2−	1495 (56.1)	10	6	0.4 (0.2 to 0.9)	7	0.5 (0.2 to 1.0)	9	0.6 (0.3 to 1.2)
All women with borderline/mild cytology	2665 (100)	132	102		119		129	

TABLE 13 Cumulative CIN3+ risks following a single HPV test at round 1 by HPV type and cytology (*continued*)

Moderate/severe cytology at round 1	Number (%) of women at baseline	Number of CIN3+ women[a]	Risk from round 1					
			2.5-year		5-year		10-year	
			Number of CIN3+ women (%)	95% CI	Number of CIN3+ women (%)	95% CI	Number of CIN3+ women (%)	95% CI
HPV 16	216 (46.8)	143	143	66.2 (59.9 to 72.4)	143	66.2 (59.9 to 72.4)	143	66.2 (59.9 to 72.4)
HPV 18	34 (7.4)	16	15	44.1 (29.4 to 62.2)	16	47.1 (32.1 to 64.9)	16	47.1 (32.1 to 64.9)
HPV 31/33/45/52/58	111 (24.0)	48	45	40.5 (32.1 to 58.3)	46	41.4 (32.9 to 51.2)	48	43.2 (34.6 to 53.0)
Other HRHPV	36 (7.8)	11	10	27.8 (16.0 to 45.5)	10	27.8 (16.0 to 45.5)	11	30.8 (18.4 to 48.7)
HC2+ non-high risk[b]	19 (4.1)	3	3	15.8 (5.4 to 41.4)	3	15.8 (5.4 to 41.4)	3	15.8 (5.4 to 41.4)
All HC2+	416 (90.0)	221	216	51.9 (47.2 to 56.8)	218	52.4 (47.7 to 57.3)	221	53.2 (48.4 to 58.0)
HC2−	46 (10.0)	5	4	8.7 (3.4 to 21.5)	5	10.9 (4.7 to 24.2)	5	10.9 (4.7 to 24.2)
All women with moderate/severe cytology	462 (100)	226	220		223		226	

a In 12 years of follow-up.
b HC2+ but no HRHPV detected.

TABLE 14 Cumulative CIN3+ risks following round 2 in women who were HC2+ with negative cytology at entry (*n* = 1120) by HPV status at round 1 and round 2

Women who were HC2+ and cytology negative entry								
			Risk from round 2					
			2.5-year		**5-year**		**10-year**	
HPV status and cytology at round 2	**Number (%) of women at round 2**	**Number of CIN3+ women**	**Number of CIN3+ women (%)**	**95% CI**	**Number of CIN3+ women (%)**	**95% CI**	**Number of CIN3+ women (%)**	**95% CI**
HC2−	806 (72.0)	2	0	0	1	0.13 (0.02 to 0.90)	2	0.26 (0.06 to 1.03)
HC2+ but no high risk detected	79 (7.1)	5	4	5.1 (1.9 to 12.9)	5	6.3 (2.7 to 14.5)	5	6.3 (2.7 to 14.5)
HRHPV+ normal cytology	158 (14.1)	14	9	5.7 (3.0 to 10.7)	11	7.0 (3.9 to 12.2)	14	8.9 (5.4 to 14.5)
Persistent HRHPV	97	13	9	9.3 (4.9 to 17.1)	11	11.3 (6.5 to 19.5)	13	13.4 (8.0 to 22.0)
New HRHPV	61	1	0	0.0	0	0.0	1	1.7 (0.2 to 11.3)
HRHPV+ borderline/ mild cytology	62 (5.5)	10	8	12.9 (6.7 to 24.2)	9	14.5 (7.8 to 26.0)	10	16.2 (9.0 to 28.0)
Persistent HRHPV	40	8	7	17.5 (8.8 to 33.2)	8	20.0 (10.5 to 36.0)	8	20.0 (10.5 to 36.0)
New HRHPV	22	2	1	4.6 (0.7 to 28.1)	1	4.6 (0.7 to 28.1)	2	9.1 (2.4 to 31.7)
HRHPV+ normal/ borderline/mild cytology	220	24						
Persistent HRHPV	137	21	16	11.7 (7.3 to 18.4)	19	13.9 (9.1 to 20.9)	21	15.3 (10.3 to 22.6)
New HRHPV	83	3	1	1.2 (0.2 to 8.3)	1	1.2 (0.2 to 8.3)	3	3.7 (1.2 to 11.0)
HRHPV+ moderate/ severe cytology	15 (1.3)	9	9	60.0 (37.2 to 83.5)	9	60.0 (37.2 to 83.5)		
Total[a]	1120 (100)	40	30		34		40	

a Ten further CIN3+ women were diagnosed before round 2 in cytology-negative HPV+ women in the revealed arm (see *Section 4: triage of human papillomavirus-positive women, particularly the interval to retesting for human papillomavirus-positive women*).

TABLE 15 Cumulative CIN3+ risks following round 2 in women with negative cytology at round 2 by HPV status at round 1 and round 2

HPV status at round 2 (negative cytology)	Number of women at round 2	Number of CIN3+ women	Risk from round 2					
			2.5-year		5-year		10-year	
			Number of CIN3+ women (%)	95% CI	Number of CIN3+ women (%)	95% CI	Number of CIN3+ women (%)	95% CI
Women with type-specific persistence								
Persistent HPV 16	41	9	7	17.1 (8.5 to 32.5)	8	19.5 (10.3 to 35.3)	9	22.0 (12.1 to 38.1)
Persistent HPV 18	13	1	1	7.7 (1.1 to 43.4)	1	7.7 (1.1 to 43.4)	1	7.7 (1.1 to 43.4)
Persistent 31/33/45/52/58	54	7	4	7.4 (2.9 to 18.5)	5	9.3 (4.0 to 20.8)	7	13.0 (6.4 to 25.3)
Persistent other HRHPV	26	0	0	0.0	0	0.0	0	0.0
Any HRHPV type specific persistence	134	17	12	9.0 (5.2 to 15.2)	14	10.5 (6.3 to 17.0)	17	12.7 (8.1 to 19.7)
Women without type-specific persistence								
New HPV 16	61	2	1	1.6 (0.2 to 11.1)	2	3.3 (0.8 to 12.5)	2	3.3 (0.8 to 12.5)
New HPV 18	32	0	0	0.0	0	0.0	0	0.0
New 31/33/45/52/58	143	3	2	1.4 (0.4 to 5.5)	2	1.4 (0.4 to 5.5)	3	2.1 (0.7 to 6.4)
New other HRHPV	114	0	0	0.0	0	0.0	0	0.0
Any new HRHPV	350[a]	5	3	0.9 (0.3 to 2.6)	4	1.1 (0.4 to 3.0)	5	1.4 (0.6 to 3.4)
HC2+ but no HRHPV	383	5	3	0.8 (0.3 to 2.4)	4	1.1 (0.4 to 2.8)	5	1.3 (0.6 to 3.2)
HC2–	12,028	12	5	0.04 (0.02 to 0.10)	7	0.06 (0.03 to 0.12)	12	0.10 (0.06 to 0.18)
HC2 results ignoring genotyping								
HC2 double positive	331	21	15	4.5 (2.8 to 7.4)	17	5.1 (3.2 to 8.1)	21	6.4 (4.2 to 9.6)
HC2 negative positive	536	6	3	0.6 (0.2 to 1.7)	5	0.9 (0.4 to 2.2)	6	1.1 (0.5 to 2.5)
HC2 positive negative	1166	2	0	0.0	1	0.09 (0.01 to 0.62)	2	0.18 (0.04 to 0.71)
HC2 double negative	10,862	10	5	0.05 (0.02 to 0.11)	6	0.06 (0.02 to 0.12)	10	0.09 (0.05 to 0.18)
All women	12,895	39	23		29		39	

a Eighty-one (23%) HRHPV+ women at round 1.

TABLE 16 Cumulative CIN3+ risks following round 2 in women with borderline or mild cytology at round 2 by HPV status at round 1 and round 2

HPV status at round 2 (negative cytology)	Number of women at round 2	Number of CIN3+ women	Risk from round 2					
			2.5-year		5-year		10-year	
			Number of CIN3+ women (%)	95% CI	Number of CIN3+ women (%)	95% CI	Number of CIN3+ women (%)	95% CI
Women with type-specific persistence								
Persistent HPV 16	13	7	7	53.9 (30.4 to 80.8)	7	53.9 (30.4 to 80.8)	7	53.9 (30.4 to 80.8)
Persistent HPV 18	8	2	2	25.0 (6.9 to 68.5)	2	25.0 (6.9 to 68.5)	2	25.0 (6.9 to 68.5)
Persistent 31/33/45/52/58	22	3	3	13.6 (4.6 to 36.6)	3	13.6 (4.6 to 36.6)	3	13.6 (4.6 to 36.6)
Persistent other HRHPV	16	2	1	6.3 (0.9 to 36.8)	2	12.5 (3.3 to 41.4)	2	12.5 (3.3 to 41.4)
Any HRHPV type specific persistence	59	14	13	22.0 (13.4 to 34.9)	14	23.7 (14.8 to 36.8)	14	23.7 (14.8 to 36.8)
Women without type-specific persistence								
New HPV 16	42	4	4	9.5 (3.7 to 23.4)	4	9.5 (3.7 to 23.4)	4	9.5 (3.7 to 23.4)
New HPV 18	17	0	0	0.0	0	0.0	0	0.0
New 31/33/45/52/58	43	3	3	7.0 (2.3 to 20.1)	3	7.0 (2.3 to 20.1)	3	7.0 (2.3 to 20.1)
New other HRHPV	35	1	0	0.0	0	0.0	1	2.9 (0.4 to 18.6)
Any new HRHPV	137[a]	8	7	5.1 (2.5 to 10.4)	7	5.1 (2.5 to 10.4)	8	5.9 (3.0 to 11.4)
HC2+ but no HRHPV	79	2	1	1.3 (0.2 to 8.7)	2	2.6 (0.6 to 9.8)	2	2.6 (0.6 to 9.8)
HC2–	304	1	1	0.3 (0.05 to 2.3)	1	0.3 (0.05 to 2.3)	1	0.3 (0.05 to 2.3)
HC2 results ignoring genotyping								
HC2 double positive	140	18	15	10.7 (6.6 to 17.1)	17	12.1 (7.7 to 18.8)	18	12.9 (8.3 to 19.7)
HC2 negative positive	135	6	6	4.5 (2.3 to 10.7)	6	4.5 (2.3 to 10.7)	6	4.5 (2.3 to 10.7)
HC2 positive negative	63	1	1	1.6 (0.2 to 10.7)	1	1.6 (0.2 to 10.7)	1	1.6 (0.2 to 10.7)
HC2 double negative	241	0	0	0.0	0	0.0	0	0.0
All women	579	25	22		24		25	

a Twenty-seven (20%) HRHPV+ women at round 1.

TABLE 17 Cumulative CIN3+ risks following round 2 by age in women with type-specific HPV persistence

| HPV status at round 2 (negative cytology)	n at round 2	n CIN3+	Risk from round 2					
			2.5-year		5-year		10-year	
			n CIN3+ (%)	95% CI	n CIN3+ (%)	95% CI	n CIN3+ (%)	95% CI
23–24								
Persistent HPV 16	14	5	5	35.7 (16.7 to 65.7)	5	35.7 (16.7 to 65.7)	5	35.7 (16.7 to 65.7)
Persistent other high-risk type	18	3	2	11.1 (2.9 to 37.6)	2	11.1 (2.9 to 37.6)	3	16.7 (5.7 to 43.2)
25–29								
Persistent HPV 16	25	8	6	24.0 (11.6 to 45.8)	7	28.0 (14.5 to 49.9)	8	32.0 (17.5 to 53.9)
Persistent other high-risk type	31	4	4	12.9 (5.1 to 30.8)	4	12.9 (5.1 to 30.8)	4	12.9 (5.1 to 30.8)
30–34								
Persistent HPV 16	16	8	8	50.0 (29.0 to 75.5)	8	50.0 (29.0 to 75.5)	8	50.0 (29.0 to 75.5)
Persistent other high-risk type	37	6	4	10.8 (4.2 to 26.3)	5	13.5 (5.9 to 29.5)	6	16.2 (7.6 to 32.6)
35–39								
Persistent HPV 16	6	1	1	16.7 (2.5 to 72.7)	1	16.7 (2.5 to 72.7)	1	16.7 (2.5 to 72.7)
Persistent other high-risk type	25	6	5	20.0 (8.9 to 41.6)	6	24.0 (11.6 to 45.8)	6	24.0 (11.6 to 45.8)
≥ 40								
Persistent HPV 16	5	0	0		0		0	
Persistent other high-risk type	39	3	3	7.7 (2.6 to 22.0)	3	7.7 (2.6 to 22.0)	3	7.7 (2.6 to 22.0)
All women								
Persistent HPV 16	66	22	20	30.3 (20.7 to 42.9)	21	31.8 (22.1 to 44.5)	22	33.4 (23.4 to 46.1)
Persistent other high-risk type	150	22	18	12.0 (7.7 to 18.4)	20	13.3 (8.8 to 19.9)	22	14.7 (9.9 to 21.5)
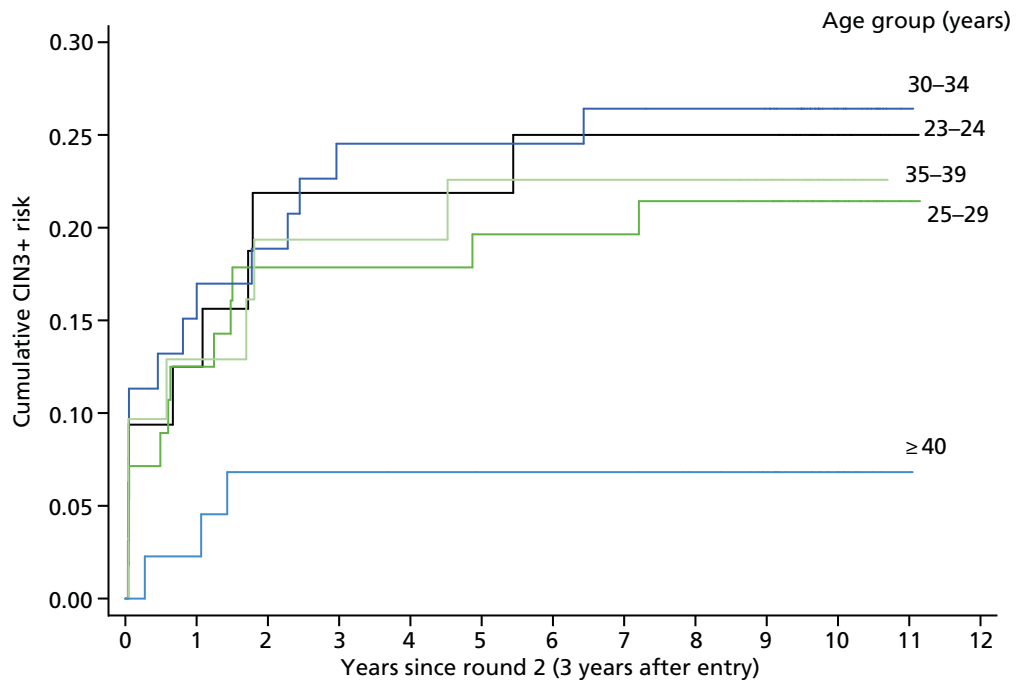
FIGURE 7 Cumulative CIN3+ risks following round 2 by age in women with type-specific persistence of any HRHPV.

Chapter 6 Discussion

Risk-based screening and cancer prevention

The UK National Screening Programme will adopt HPV screening and triage protocols that strike an acceptable balance between cancer risk and the cost and patient inconvenience of excessive screening and referral rates and unnecessary treatment. Acknowledging that there is no such thing as zero risk, Castle et al.[18] proposed a risk-based strategy for cervical screening based on widely accepted practice, and suggested that women should be returned to routine screening if they have a < 2% CIN3+ risk, recalled earlier than the routine screening interval if they have a 2–10% risk, and referred to immediate colposcopy if they have a > 10% risk. These specific cut-off points may be considered arbitrary and do not consider the relationship between CIN3 and cancer risk. The aim of screening is to prevent invasive cancer and not CIN3; therefore, the acceptable cumulative CIN3+ risk when a woman is next screened depends on the ratio of cancer risk to CIN3 risk at the next screen. This ratio depends mainly on the delay between time of development of CIN3 during the screening interval and its treatment when it is detected at the next HPV test or after subsequent triage processes.

Many CIN3 cases develop soon after HPV acquisition and most develop within a few years.[19] Therefore, the CIN3 incidence rate in women who were HPV– at their last test is approximately proportional to their age-specific incidence rate of new HPV infection (with a lag of a year or two), and, hence, proportional to the overall population HPV prevalence (*Figure 8*), as most prevalent infections are newly acquired and transient even in older women (see *Table 3*).

The cumulative CIN3 risk at next screen is also roughly proportional to the screening interval (*Figure 9*). The cervical cancer incidence rate in women with untreated CIN3 appears to be fairly constant at about 1% per year, independent of age,[1] so the cancer risk at next screen should be roughly proportional to the square of the screening interval. In unscreened populations with fairly constant HPV infection rates up to middle age, cervical cancer incidence should therefore rise linearly from age at first intercourse. From 10 to 30 years after first intercourse, the observed quadratic relationship corresponds closely to a linear increase with a diagnostic lag of 7.5 years.[20] In primary screening, women who test HPV– acquire new infections and develop resulting CIN3 throughout the interval to next test. In contrast, in the further interval before retesting when HPV+

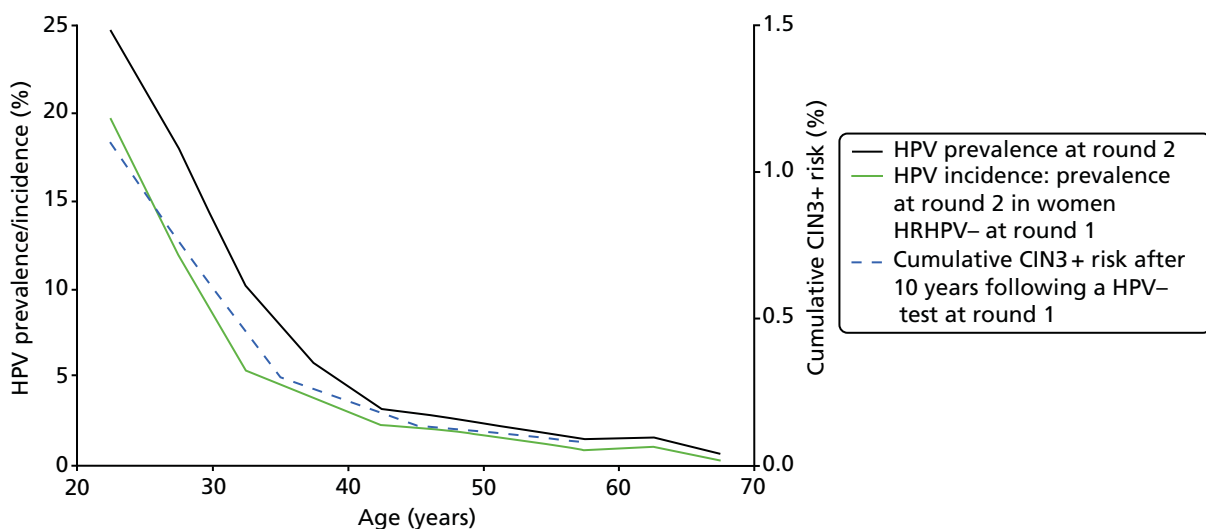**FIGURE 8** Age-specific HRHPV prevalence at round 2 by age at round 2 overall and in women who were HRHPV– at round 1, and cumulative 10-year CIN3+ risk by age at round 1 in women who were HC2– at round 1. (HRHPV prevalence rates at round 2 by age at round 1 in women who were HRHPV– at round 1 in 5-year age groups from 20–24 years to 55–59 years were 14.7%, 8.1%, 3.6%, 2.9%, 2.2%, 1.5%, 1.5% and 0.8%.)

women are being triaged, most CIN3 lesions will have developed long before or soon after their positive HPV test. Therefore, some cancers will be present at the screening visit when HPV is detected, and the cancer risk will further increase at a roughly constant rate throughout the triage process. This simplified and speculative model ignores several relevant factors, including the lag from HPV acquisition to CIN3 development and the rate of progression to detectable cancer, but it illustrates the weakness of screening and triage protocols based only on CIN3+ risk. An undefined model of cancer risk underlies the focus on CIN3 that informs cervical screening and triage protocols. An explicit model based on epidemiological knowledge should perhaps be developed and refined as an alternative basis for cost–benefit evaluation of the details of HPV screening and triage protocols, as it is unlikely that their effects on cancer incidence can be observed directly. Even the simple comparison of HPV testing against cytology required the pooled results of trials with a total of 176,000 randomised women to detect the effect on cancer incidence.[6]

The long-term protection of a negative human papillomavirus test and, hence, the safe screening interval at different ages

The 10-year CIN3+ rate among women who were HPV– at entry to ARTISTIC is only 0.1% in those aged ≥ 40 years, suggesting that screening intervals for HPV– women aged 40–49 years might be extended even further than the 6 years previously suggested.[4] Our data are consistent with the long-term risks reported from women participating in the POBASCAM trial in the Netherlands that has led to the recommendation for the Dutch HPV screening programme to adopt a 10-year screening interval in women aged ≥ 40 years.[21] Many HPV– women have had an earlier infection, so this very low long-term risk after a single negative HPV test suggests that a HPV infection that has become undetectable rarely recurs and then progresses to CIN3. Frequent HPV testing, therefore, greatly increases the number of transient infections that are detected without increasing sensitivity for CIN3 detection.

As noted above, if most CIN3 cases (and a large proportion of CIN2 cases) persist, then their prevalence will increase almost linearly with increasing screening interval. This was seen in routinely screened women in Manchester in the 1990s, in whom CIN3 prevalence increased almost linearly with longer intervals since last normal cytology.[22] Age-standardised CIN2+ prevalence in ARTISTIC shows this pattern at round 2 (*Figure 9*), with an annual increase of about 0.2% per year since entry in women with a cytologically normal entry test. *Figure 9* shows that CIN2+ prevalence at entry increased at a similar rate with increasing
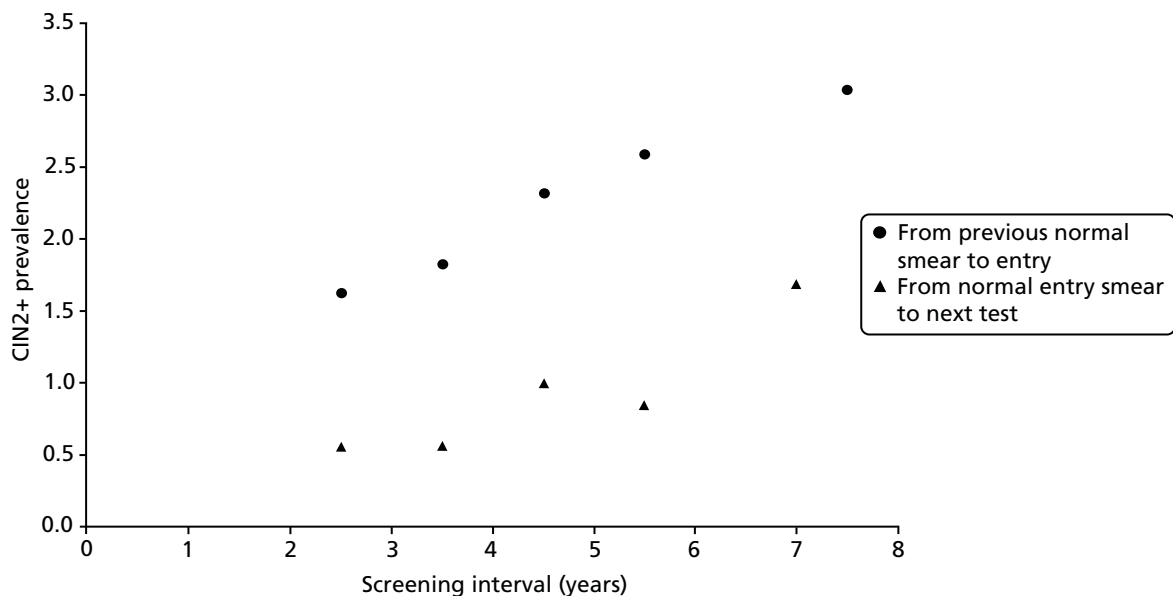

FIGURE 9 Age-standardised prevalence (%) of CIN2+ during ARTISTIC by time since previous normal cytology to entry, and by time since cytologically normal entry to next test. Women whose previous cytology was abnormal or < 2 years before entry are excluded.

interval from the previous normal cytology to entry, with the addition of about 1.2% reflecting the CIN2+ prevalence missed by previous screening rounds that was detected at entry to ARTISTIC.

The role of human papillomavirus typing

The HPV+ women with borderline/mild cytology as well as those with negative cytology might be further triaged by HPV type to identify those who can be recalled later. A HPV test that identifies HPV types 16, 18 and 31/33/45/52/58 would enable this moderate-risk subgroup, which constitutes 58.4% of HPV+ women with borderline/mild cytology, to be referred immediately or followed up within (say) 1 year. See *Table 13*, which shows the 5-year CIN3+ risks of 10.9%, 4.1% and 2.9% with negative cytology, and 20.9%, 10.8% and 9.4% with borderline/mild cytology. Borderline/mild cytology with other HRHPV types (35, 39, 51, 59 and 68) has a 5-year CIN3+ risk of 3.5% and might be recalled 3 years later for a repeat HPV test. Immediate referral or early retesting of women with HPV 16 was recently recommended in the Netherlands[23] and proposed more than 10 years ago in the USA,[24] but the cost–benefit balance of more complex triage protocols based on full HPV typing following cytology triage deserves further consideration, particularly for vaccinated women. *Table 13* shows that most of the CIN3+ risk in HPV+ women with abnormal cytology is present at, or soon after, HPV detection and increases by about only 2% from 2.5 to 10 years irrespective of cytology.

Triage and referral policy in relation to primary screening interval

Figure 9 confirms that the marked reduction from round 1 to round 2 in the proportion of HC2+ women aged ≥ 25 years who had moderate+ cytology (11.2% and 3.2%, respectively; see *Table 6*) reflects the elimination of long-standing high-grade disease that had been missed at previous routine cytology. The round 1 results, thus, represent what might be seen in primary HPV testing with a very long screening interval, whereas round 2 shows results after an interval of about 3 years. However, the overall CIN3 risks in HRHPV+ women were almost the same after stratifying by cytology, with 5-year CIN3 risks for normal, borderline/mild and moderate+ cytology of 3.1%, 9.5% and 52.4%, respectively, in round 1, and 2.5%, 8.4% and 44.7%, respectively, in round 2. This suggests that recall policy following cytology triage of HPV+ women need not depend on the primary screening interval.

Triage and referral policy in relation to type-specific human papillomavirus persistence

Table 12 shows that the 10-year CIN3 risk for women with a new HPV type at round 2 was only 3.4% (95% CI 2.1% to 5.4%). The risk was no higher in those whose HPV infection at round 1 had cleared (2.7%, 95% CI 0.9% to 8.0%) than in those who were HPV– at round 1 (3.6%, 95% CI 2.2% to 6.0%). In contrast, the 10-year CIN3 risk in women with type-specific persistence at round 2 is six times greater than for a new infection of the same type. Among 331 women with HRHPV at both rounds, 58% had the same type (10-year CIN3 risk 20.4%, 95% CI 15.6% to 26.4%). The 10-year CIN3 risk in the remaining 42% who had cleared the original type and acquired a new type was only 2.7%, so these women could safely be recalled 3 years later when most of their infections will have cleared. This large difference in risk (*p* < 0.0001), and, hence, the potential efficiency of further triage, is diluted with HPV tests that do not identify all 13 high-risk types. The price of different HPV tests and the disadvantages of more complex triage and referral protocols will determine whether or not the advantages of full HPV typing outweigh the costs.

A triage protocol in which women are recalled repeatedly until their CIN3 risk exceeds (say) 10% implies a cycle of repeated testing that ends only in HPV clearance or referral, and some limit must be set to detect and treat occult CIN3 that has regressed cytologically. A HPV infection that has persisted for 5 years should

perhaps be referred for random cervical biopsy. In a prospective study in the Netherlands, six out of the eight women with untreated CIN who regressed to normal cytology and colposcopy but remained HRHPV+ over several years had occult CIN3 detected by random biopsy.[25]

We excluded women with any recorded histology in calculating HPV clearance rates, as biopsy can induce clearance.[26] This might lead to an overestimate of clearance but, as the clearance rates for new and persistent HRHPV infections shown in *Table 4* are similar to those reported by Nobbenhuis *et al.*[27] in women followed up without intervention, any bias seems to be small.

Triage of human papillomavirus-positive women

If the screening interval is increased, the time between appearance and diagnosis of CIN3 and, hence, the risk of progression to cancer will also increase, so the triage protocol must minimise the delay in referring those at highest risk to colposcopy. Nonetheless, the evidence from round 1 of ARTISTIC (see *Table 13*) indicates that the triage protocol being piloted in England could be too conservative, at least for HPV+ women with negative cytology. The risk of developing CIN3 within 5 years in HPV+ women is 52.4% for moderate/severe cytology, 9.6% for borderline/mild cytology and only 3.1% for normal cytology (see *Table 13*). The suggestion that a CIN3+ risk of about 10% is a reasonable threshold for immediate colposcopy[18,28] would, therefore, imply rapid referral for HPV+ women with any abnormal cytology except perhaps the minority of women with borderline/mild cytology who have genotypes with the lowest associated risks. The minimal increase in the risk of developing cancer by retesting women with borderline/mild cytology rather than referring them directly to colposcopy has always been accepted, and it is not clear that this risk/benefit balance should be abandoned when they are found to have HPV. In round 1 of ARTISTIC, the proportion of HPV+ women with moderate + cytology was 12% below age 50 years and at age 50 years or older. By round 2 of ARTISTIC, only 5% of HPV+ women aged < 50 years and 1% of women aged ≥ 50 years had moderate/severe cytology. The majority of HPV+ women in a population regularly screened by HPV testing will, thus, have negative or borderline/mild cytology.

Triage: women with normal cytology

Of the women who were HC2+ with normal cytology at entry to ARTISTIC, 72% had cleared their HPV infection within 3 years (see *Table 14*). Only 1.3% (15 out of 1116) of women had moderate or worse cytology by round 2 (of whom, nine were diagnosed with CIN3). Fourteen per cent of women remained HPV+ with normal cytology, but approximately 60% of these (97 out of 158) had type persistent HPV and approximately 40% (61 out of 158) had new HPV types. The subsequent elevated cumulative risk was among those with type-specific infections. This also applied to those with borderline/mild cytology at the follow-up, but this was based on small numbers. This implies that the current policy in the pilot sites (repeat testing after 1 year and referral to colposcopy after 2 years if women are still HPV+ with normal cytology) is referring a large proportion of women to unnecessary testing and colposcopy. Recall after 2 or 3 years then referring only those developing moderate+ cytology and those with type-specific persistence may be a better strategy.

Triage: women with borderline/mild cytology

Among HPV+ 24- to 64-year-old women presenting with borderline/mild cytology at entry, 29% had cleared their HPV infection within 1 year and an additional 19% remained HPV+ but became cytologically normal. Those with HPV 16 with 5-year CIN3+ risk of 20.5% should clearly be referred immediately, but inviting all HPV+ women with borderline or mild cytology to return for a repeat test at 1 year would substantially reduce immediate referrals and could be a better strategy.

Ages at starting and stopping screening

Stopping screening

The effect on long-term CIN3+ risk of stopping screening in women who are HPV– at various ages can be inferred from *Table 10*. For example, the 10-year CIN3+ risk in HPV– women aged ≥ 50 years is only 0.1%. Their risk of acquiring HPV is an order of magnitude lower than for women aged 20–24 years (see *Table 3*), and there is plausible epidemiological evidence that HPV infection in middle age confers little lifetime risk of cervical cancer.[20] Conversely, the case for a further test at least 10 years later is that their lifetime cancer risk could also be of the order of 1 per 1000 and possibly higher. The sharp decline with increasing age in the CIN3-to-cancer ratio in ARTISTIC (see *Table 8*), and the observation that CIN3 that remains detectable by HPV testing and random biopsy can regress to become cytologically and colposcopically undetectable[25] suggests that their CIN3 risk may be underestimated. A quirk of the current screening protocol is that a woman's age at her final test ranges from 60 to 64 years because the final invitation is 5 years after her previous test unless this was at age 60 years or older. One final test at the age of 65 years could be offered to all women who were HPV– at the age of 50 years. Whatever the age at stopping, the final HPV test might require a more sensitive test than at younger ages. Five out of the six women in ARTISTIC who developed invasive cervical cancer after a negative HC2 entry test were found to be HRHPV+ when the stored entry sample was retested by PCR. Alternatively, HPV and cytology cotesting might be considered at a woman's final test. The one woman in ARTISTIC and all three in the POBASCAM trial[21] who developed invasive cancer within 4 years of a HPV– entry test were cytologically abnormal at entry.

Age at starting screening

The natural history of HPV infection, persistence and progression to CIN3 is similar at all ages from 20 years to about 45 years, after which the CIN3 rate in HPV+ women falls (see *Figure 7*) and cervical cancer incidence in unscreened populations shows a sharp inflection.[20] Therefore, the age at which screening begins (currently 25 years) might be reconsidered when HPV testing is introduced. Owing to this, we have outlined some of the effects of beginning HPV screening at (say) age 22 years to illustrate the issues involved. Screening after age 25 years reduces cervical cancer incidence, particularly for more advanced disease;[2] therefore, earlier screening would presumably achieve some reduction in the rising cancer incidence in young women. The effect on referrals to colposcopy would depend on whether immediate referral was restricted to women with moderate or severe cytology, and on the recall interval for HPV+ women with normal, borderline or mild cytology. Almost 40% of women aged 20–24 years were HC2+ at entry to ARTISTIC, but only 4.2% had moderate or severe cytology.[3] A second test at age 25 years for those who were HPV+ at age 22 years would enable type-specific persistence to be identified and triaged. As discussed above, the CIN3+ risk is much lower in those with a new HPV infection; therefore, they could safely be recalled 3 years later, when most infections will have cleared, except perhaps those with HPV 16 (see *Table 12*).

Study limitations

The effect of cervical sampling and biopsy on human papillomavirus clearance

A potential bias in the observed 10-year cumulative CIN3+ rates in HPV– women is the possibility that intervening screening, biopsy and treatment could have induced clearance of subsequent HPV infections and prevented progression to CIN3.[26]

Variation in cytology practice

ARTISTIC recruited from 127 centres spread throughout the Greater Manchester area and cytology was performed in two laboratories where the staff were retrained ahead of the national roll-out of LBC, which improved the sensitivity of our cytology,[10] as this varies between laboratories. The HC2 test used in ARTISTIC has largely been replaced for use in the NHS by modern PCR-based assays. We do not know how these assays would have performed, particularly in detecting HPV among women who tested HC2– at entry but subsequently developed invasive cervical cancer (see *Table 7*). Despite these potential issues, we have shown similarities between the first round of ARTISTIC and the national pilot study (see *Table 6*) and believe the results to be generalisable to the British population.

Hybrid capture 2 test sensitivity

Table 2 shows that about 4% of samples from women aged ≥ 25 years who tested positive for HPV by HC2 showed no HRHPV on genotyping. These constituted over half of HC2+ results in women aged ≥ 50 years. A total of 40% of these women had a RLU of between 1 and 2 pg/μl, indicating that most are probably false positives.[11] (The definition of HC2 test positivity is a RLU of ≥ 1 pg/μl.) Our conclusions are unlikely to have been much affected by ignoring these women who were HC2+ but negative for the 13 high-risk target types (4.2% of all women in round 1 and 3.5% in round 2; see *Table 2*). Their 10-year CIN3 rate was 1.8% (3.0% in those with low-risk HPV types and 0.8% in those negative for all 27 HPV types identified by the linear array), and their inclusion in the HC2– group would increase the 10-year CIN3+ risk in HC2– women from 0.31% to 0.37%. Low-risk HPV types occasionally cause high-grade neoplasia but by definition are not associated with invasive cancer risk, so the proportion of high-grade CIN cases that are missed by HRHPV testing is not an indication of inadequate sensitivity. Modern PCR-based HRHPV tests may have slightly better sensitivity with respect to cancer than the HC2 test.

Human papillomavirus-negative cancers

The small proportion of cervical cancers that do not contain HPV DNA will be missed by any HPV-based primary test. Only 0.3% were HPV– in an international series of cancer biopsies with stringent criteria for diagnosis and PCR adequacy and separate PCR assays for each high-risk type.[29] A more relevant estimate for the practical purpose of improving routine screening is the proportion of cancers in which HPV cannot be detected in recent cervical samples. None of the latest available samples before diagnosis from the 23 cancers in this cohort was HPV– on retesting, but *Table 7* shows that the entry sample was HC2 negative but HPV positive by PCR in 5 (22%). Larger numbers tested by standard modern assays will provide a more precise estimate of this important index of sensitivity.

Further research

The National Institute for Health Research has funded a further extension, under which follow-up for CIN2 diagnoses (which are managed clinically in the same way as CIN3 but are not recorded centrally) will be updated through local histology laboratories. The sample bank, augmented by further samples from women in the cohort who are screened between 2018 and 2022, will be used to retest samples from women who develop CIN3 or cancer and matched controls. Interim results for CIN2+ as well as CIN3+ will be provided to the NSC in order to inform its recommendations on screening intervals for HPV– women and triage protocols following HPV detection. The same data would be available in the future from national routine screening records if these were linked to histology records to capture CIN2 diagnoses as well as to national cancer registration. The establishment of a larger national bank of samples from routinely screened women would provide much larger numbers of samples from women who will develop cervical cancer for retesting by more sensitive PCR and with alternative screening or triage assays such as DNA methylation.

Conclusions

A screening interval of up to 10 years following a negative HPV test might be considered for women aged ≥ 40 years and perhaps for younger women following a negative HPV test. Immediate referral of all HPV+ women with mildly abnormal cytology, as adopted in the English pilot study of primary HPV screening, may not be essential and recall intervals of 1 year for high-risk subgroups and 3 years for the remainder could be considered. The risk is largely confined to women with a persisting type-specific HPV and a 10-year interval will identify them efficiently. The possibility of a small increase in risk of progression to invasive cancer between screening rounds and perhaps some increase in the proportion of women who fail to attend regularly must be weighed against the advantages for patients and reduction of NHS costs with longer screening intervals.

Routine HPV testing and follow-up to HPV clearance will divide the population into the low-risk HPV–majority and those with type-specific persistent HPV infection among whom virtually all cervical cancers will arise. Those whose infections do not disappear after repeated testing may consider curative treatment irrespective of cytological or colposcopic findings, particularly when they reach the age at which routine screening ends.

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Ms Clare Gilham (Medical Statistician) carried out the data management and statistical analysis and drafted the report.

Dr Alexandra Sargent (Clinical Scientist) conducted the virology testing for ARTISTIC.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to available anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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