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

Clare Gilham,[1] Alexandra Sargent,[2] Henry C Kitchener[3] and Julian Peto[1]*

[1]Non-Communicable Disease Epidemiology Unit, London School of Hygiene & Tropical Medicine, London, UK
[2]Department of Virology, Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK
[3]School of Cancer and Sciences, University of Manchester, St Mary's Hospital, Manchester, UK

*Corresponding author julian.peto@lshtm.ac.uk

Declared competing interests of authors: Henry Kitchener reports grants from the University of Manchester during the conduct of the study. He is chairperson of the Advisory Committee for Cervical Screening (Public Health England) as well as of the National HPV Pilot Steering Group. Any views expressed in this report are those of the authors and not of Public Health England.

Published June 2019
DOI: 10.3310/hta23280

Scientific summary

ARTISTIC RCT: follow-up

Health Technology Assessment 2019; Vol. 23: No. 28
DOI: 10.3310/hta23280

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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 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

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.513

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the Clarivate Analytics Science Citation Index.

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 98/04/501. The contractual start date was in September 2013. The draft report began editorial review in April 2017 and was accepted for publication in November 2017. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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