ARTISTIC: a randomised trial of human papillomavirus (HPV) testing in primary cervical screening

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Executive summary

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Executive summary

Objectives

Primary cervical screening is currently based on using cervical cytology to detect cancer precursor lesions. Human papillomavirus (HPV) testing could add sensitivity to the detection of these lesions [cervical intraepithelial neoplasia stage 3 or beyond (CIN3+)] either as an adjunct to cytology, or as a first test with cytology reserved for women who are HPV positive. We aimed to answer the following principal questions:

- Do cytology and HPV testing combined achieve a reduction in incident CIN3+ by detecting significantly more prevalent disease?
- Is the use of HPV testing cost-effective in primary cervical screening?
- Is HPV testing in primary cervical screening associated with adverse psychosocial or psychosexual effects?
- How would HPV perform as an initial screening test followed by cytology for HPV positivity?

Design

ARTISTIC was a randomised trial of cervical cytology versus cervical cytology plus HPV testing, evaluated over two screening rounds, 3 years apart. Round 1 would detect prevalent disease and round 2 a combination of incident and undetected disease from round 1.

Setting

Women undergoing routine cervical screening in the NHS programme were recruited in general practices and family planning clinics in Greater Manchester.

Participants

In total 24,510 women aged 20–64 years were enrolled between July 2001 and September 2003.

Interventions

HPV testing was performed on the liquid-based cytology (LBC) sample obtained at screening. Women were randomised in a ratio of 3 : 1 either to have the HPV test result revealed and acted upon if persistently positive in cytology-negative cases, or concealed from the woman, her doctor and the investigators. In addition, a detailed health economic evaluation and a psychosocial and psychosexual assessment were performed.

Main outcome measures

The primary outcome was CIN3+ in round 2. Secondary outcomes included an economic assessment and psychosocial effects. We have also conducted a large HPV genotyping study.

Results

In round 1 there were a total of 313 CIN3+ lesions representing a prevalence in the revealed and concealed arms of 1.27% and 1.31% respectively ($p = 0.81$). Round 2 involved 14,230 women (58.1%) of those screened in round 1. In round 2, (30–48 months) only 31 CIN3+ were detected and although the CIN3 rate was lower in the revealed arm (0.18% revealed versus 0.34% concealed; $p = 0.09$), this was not statistically significant. A less restrictive definition of round 2, (26–54 months) increased the CIN3+ numbers in round 2 from 31 to 45, with a statistically significant reduction in CIN3+ incidence in the revealed arm (0.24% revealed versus 0.41% concealed; $p = 0.05$). There was no difference in CIN3+ between the arms when round 1 and 2 were combined (1.45% revealed versus 1.65% concealed; $p > 0.1$). Among 2226 women who screened as cytology negative and HPV positive in round 1, 32 CIN2+ lesions were detected among the 1657 women in the revealed arm as a consequence of adjunctive HPV testing. This resulted in a lower CIN2+ rate in the revealed arm in round 2 (30–48 months; 1.92% versus 3.99%; $p = 0.06$), which just failed to reach significance.

The prevalence of high-risk types was highly age-dependent: 27.9% in women aged 25–29 years compared with 6.5% at age 50–64 years. The overall prevalence of HPV type 16 and/or type 18 in borderline, mild, moderate and severe dyskaryosis was 10.0%, 22.0%, 46.8% and 62.4% respectively. Type-specific viral persistence rates declined from over 80% after 6 months to 20–25% after 48 months.

Mean (SD) costs per woman (covering screening and colposcopy-related events) in round 1 were £72 (£175), [95% confidence interval (95% CI), £70 to £75] for the revealed arm and £56 (£178), (95% CI, £52 to £60) for the concealed arm ($p < 0.001$). Costs were age-dependent, so an age-adjustment based on the age profile for the national screening programme reduced the mean costs to £65 and £52 respectively. The incremental cost-effectiveness ratio for detecting an additional CIN3+ by the addition of HPV testing to LBC screening in round 1 was £38,771. The experiences of revealed women in round 1 informed the development of alternative screening policies with simplified management protocols. An age-adjusted mean cost for LBC primary screening with HPV triage was £39 compared with £48 for HPV primary screening with LBC triage, the main influence on the costs being the rates of referral for colposcopy.

HPV testing did not appear to cause significant psychosocial distress.

Conclusions

Routine HPV testing did not add significantly to the effectiveness of LBC in this study. The use of LBC was associated with an unexpectedly low number of CIN3+ lesions in round 2, suggesting an increase in sensitivity compared to conventional cytology. No significant adverse psychosocial effects were detected, which is reassuring for the wider use of HPV testing. It is clear that it would not be cost-effective to screen with cytology and HPV combined but there was evidence that HPV testing, either as a triage or as an initial test triaged by cytology, would be cheaper than the current use of cytology without HPV testing.

The introduction of HPV vaccination against types 16/18 for 12- to 13-year-old girls in 2008 will reduce the risk of the most severe abnormalities in vaccinees by 65% but only 10–20% of low-grade cytological abnormalities will be prevented.

The ARTISTIC findings suggest that LBC, which has been implemented countrywide, would not benefit from combined testing with HPV. While LBC is highly effective as primary screening, HPV testing has the twin advantages of a high negative predictive value, which should allow longer screening intervals, and automated platforms enabling high throughput. HPV primary screening would have a major impact on the volume of cytology, which would require major contraction and reconfiguration of laboratory services.

Further research

There is a need to confirm from other UK laboratories, the finding in the ARTISTIC cohort of a very low incidence of CIN3+ in subsequent screening rounds of women previously screened with LBC. This would suggest that LBC in the quality-assured setting of the NHS can indeed achieve a greater degree of sensitivity than hitherto recognised.

The ARTISTIC trial is continuing to follow up women while maintaining the randomised concealment of HPV testing results for a further 3-year round of screening. This will allow evaluation of the risk of developing cytological abnormalities in type-specific HPV-positive and HPV-negative women over a 6-year interval, which will be important in developing screening protocols for the post-vaccination era, when the case for initial HPV testing with cytology triage will become stronger. The 6-year follow-up will also provide data on the relative protection of a negative cytology and negative hybrid capture 2 over 6 years in different age ranges.

Publication

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NIHR Health Technology Assessment programme

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