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Title **ARTISTIC: A Randomized Trial of Human Papillomavirus (HPV) Testing in Primary Cervical Screening**

Agency **NETSCC, HTA, NIHR Evaluation and Trials Coordinating Centre**
Alpha House, University of Southampton Science Park, Southampton, SO16 7NS, United Kingdom;
Tel: +44 2380 595 586, Fax: +44 2380 595 639; hta@soton.ac.uk, www.hta.ac.uk

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Aim

To determine if human papillomavirus (HPV) testing adds significant sensitivity to liquid-based cytology (LEC) in primary cervical screening.

Conclusions and results

Round 2 involved 14 230 women (58.1%) who had been screened in round 1. There was no statistical difference in the detection of CIN3+ between the concealed and revealed arms in either round 1, round 2, or rounds 1 and 2 combined. In round 1, there were 313 CIN 3+ (233 revealed versus 80 concealed; p=0.81) and in round 2 there were only 31 CIN3+ (19 revealed versus 12 concealed; p=0.08) among women who were cytology -ve and HPV +ve in round 1. There was a statistically significant lower rate of CIN2+ (but not CIN3+) in the revealed arm in round 2 (p=0.036). Only 10 CIN3+ lesions were detected in round 1 as a direct consequence of adjunctive HPV testing. The prevalence of high-risk types was age-dependent: 27.9% in women aged 25 through 29 years compared with 6.5% aged 50 through 64 years. The prevalence of HPV 16 and/or 18 in borderline, mild, moderate, and severe dyskaryosis was 10.0%, 22.0%, 46.8%, and 62.4% respectively. Viral persistence rates decline from over 80% at 6 months to 20% to 25% over 48 months. Mean (SD) costs per woman in round 1 were 72 pounds sterling (GBP) (GBP 175) for the revealed arm and GBP 56 (GBP 178) for the concealed arm (p<0.001). As costs were age-dependent, an age adjustment based on the age profile for the national screening program reduced the mean costs to GBP 65 and GBP 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 GBP 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 GBP 39 compared with GBP 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.

Recommendations

HPV testing did not add significantly to the effectiveness or cost effectiveness of LBC in this study. An unexpectedly low number of CIN 3+ lesions in round 2 suggested a marked increase in sensitivity compared to conventional cytology. No significant adverse psychosocial effects were detected. It would not be cost effective to screen with cytology and HPV combined, but HPV testing either as a triage or as an initial test triaged by cytology appears to be cheaper than the current use of cytology without HPV testing.

Methods

See Executive Summary link at www.hta.ac.uk/project/1162.asp.

Further research/reviews required

The low incidence of CIN 3+ in the ARTISTIC cohort needs to be confirmed in a subsequent screening round of women previously screened with LBC. Confirmation from other UK laboratories would suggest that LBC can achieve greater sensitivity in the quality assured setting of the NBS. The ARTISTIC trial continues to follow women while maintaining the randomized concealment of HPV testing results. This will allow evaluation of the type-specific risk of developing cytological abnormalities in HPV-positive women with negative baseline cytology, which will be important in developing screening protocols for the post-vaccination era when the case for initial HPV testing with cytology triage will be stronger. Such an approach would require an effective and cost effective means of managing HPV-positive/cytology-negative women.

Written by Professor Henry Kitchener, NETSCC, United Kingdom

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