What is an evidence note

Evidence notes are rapid reviews of published secondary clinical and cost-effectiveness evidence on health technologies under consideration by decision makers within NHSScotland. They are intended to provide information quickly to support time-sensitive decisions and are produced in an approximately 3 month period. Evidence notes are not comprehensive systematic reviews. They are based on the best evidence that Healthcare Improvement Scotland could identify and retrieve within the time available. The reports are subject to peer review but do not undergo external consultation. Evidence notes do not make recommendations for NHSScotland.

Introduction

Human papillomavirus (HPV) is a sexually-transmitted virus. Most HPV infections clear through the natural immune response. Persistent infection with high-risk subtypes (particularly 16 and 18) can lead to cervical cancer.

Internationally, there is variation in approach to screening for cervical cancer. Many countries, including Scotland, have organised screening programmes; although these differ in age range, screening interval, test and protocol. Countries without organised programmes may screen opportunistically or not at all.

HPV testing is not currently undertaken in the Scottish Cervical Screening Programme. In Scotland, women aged 20–60 years are invited to attend for a smear test every 3 years. Liquid-based cytology (LBC) is used to detect precancerous squamous cell changes. It may also reveal glandular abnormalities. Women with moderate dyskaryosis or more severe cytological abnormalities are referred to colposcopy. Initial borderline and mildly dyskaryotic results are followed up by repeat smears. Women with three borderline or two mild results at follow up are referred to colposcopy.

During colposcopy, a biopsy may be taken to diagnose cervical intraepithelial neoplasia (CIN) or cervical glandular intraepithelial neoplasia (cGIN). CIN is graded 1, 2 or 3. CIN1 affects the lower third of the surface and is considered low grade. CIN2 affects the lower two thirds. CIN3 affects the full thickness, and includes carcinoma in situ. CIN2, CIN3 and most cases of cGIN are considered high grade. High-grade lesions can progress to cancer and are therefore treated. Results at least as serious as CIN2, including cancer, are collectively denoted CIN2+. Results at least as serious as CIN3, including cancer, are collectively denoted CIN3+. Lower grades of lesion may resolve spontaneously and not require clinical intervention, but do require follow up.

Key points

- In primary screening for cervical cancer, HPV testing followed by conventional cytology triage of positive results is highly sensitive and highly specific for the detection of CIN3+ (CIN3, carcinoma in situ and cervical cancer).
- HPV testing followed by conventional cytology triage of positive results is more sensitive than cytology alone for the detection of CIN3+.
- In women 35 years and older, HPV testing followed by conventional cytology triage of positive results is more specific than cytology alone. More evidence is required to establish relative specificity in women aged 20–35 years.
- Primary HPV testing allows the screening interval to be safely extended to at least 6 years.
- Primary HPV testing followed by conventional cytology triage of positive results, with a 5-year screening interval, may be cost effective compared with 3-yearly conventional cytology.
Advancement of knowledge and technology in relation to HPV has prompted consideration of the potential utility of HPV testing at various stages of the Scottish Cervical Screening Programme. ‘Test of cure’ — HPV testing after treatment of CIN2+ — is being implemented in Scotland in 2012, to allow women’s earlier return to routine screening. This evidence note reviews published evidence on the clinical and cost effectiveness of HPV testing, followed by LBC triage of positive results, in primary screening for cervical cancer. Research literature on HPV testing for triage of mild, borderline and unsatisfactory smears is reviewed in evidence note 42.

Health technology description

High-risk HPV testing entails the laboratory analysis of cervical samples to detect oncogenic types of HPV deoxyribonucleic acid (DNA). The Hybrid Capture II (HC2) (QIAGENE, Gaithersburg, MD) test uses a nucleic acid hybridisation assay with signal amplification using chemiluminescence for detection of 13 genotypes associated with high risk of cervical cancer. Samples are considered positive at relative light units to control of at least 1.0 pg/ml. The APTIMA® HPV (AHPV) assay (Gen-Probe, San Diego, CA) uses target capture, transcription-mediated amplification and dual kinetic assay to detect 14 high-risk types of viral E6 and E7 mRNA oncoproteins. Samples are considered positive if the signal to cut-off ratio is at least 1.0. Non-commercial polymerase chain reaction (PCR) methods are also used.

Epidemiology

Cervical cancer is newly diagnosed in around 300 women per year in Scotland and accounts for around 100 deaths per year3. The peak incidence occurs when women are in their 40s1. Women from more deprived areas have an increased chance of developing, and dying from, cervical cancer3. Smokers are at increased risk due to genetic and immune response changes, and reduced effectiveness of treatment4.

The peak incidence of HPV infection occurs around age 20 years1. Prevalences of high-risk HPV reported in 2006 from the ARTISTIC trial, set in Manchester, England, were 40% at age 20–24 years, 28% at age 25–29 years, 18% at age 30–34 years, 12% at age 35–39 years, 9% at age 40–44 years, 8% at age 45–49 years, 7% at age 50–54 years and 6% at both 55–59 years and 60–64 years5.

The epidemiology of cervical cancer in Scotland is expected to change over the next few decades. The introduction in 2008 of the HPV vaccination programme targeting adolescent girls is likely to reduce incidence and mortality. As vaccinated cohorts enter the Scottish Cervical Screening Programme, reductions in the number of positive smears and colposcopies are anticipated. A reduction in positive smears may, due to the repetitive and subjective nature of cytology, lead to a decline in test performance1.

Clinical effectiveness

The intervention and comparator of interest in this evidence note are screening protocols — relating to specific ‘packages’ of primary test, screening interval, triage test, and follow-up protocol — rather than individual tests. There are many possible combinations of these aspects in practice. There is also between-country variation in screening age range and coverage. No studies were found which directly addressed the research question of whether HPV testing, followed by LBC triage of positive results, is clinically and cost effective in primary screening for cervical cancer compared with current Scottish practice of 3-yearly screening using LBC.

The newness of the technology means that few studies have sufficient long-term data on cervical cancer incidence and mortality. Intermediate outcomes of CIN2+ and CIN3+ are generally reported.

The most applicable evidence comes from a 2011 systematic review by the Agency for Healthcare Research and Quality addressing a number of questions in relation to cervical cancer screening, including primary HPV testing followed by cytology triage of positive results6.

A single randomised controlled trial (RCT) was included of 71,337 women in Finland aged between 25–65 years invited for 5-yearly screening using HC2 triaged by conventional cytology versus conventional cytology alone7-10. Women with cytology results of Papanicolaou class III or IV (equivalent to at least as severe as mild dyskaryosis) were referred to colposcopy. Women with cytology results of Papanicolaou class III or IV (equivalent to at least as severe as mild dyskaryosis) were referred to colposcopy. Women with cytology results of Papanicolaou class II (equivalent to borderline) were followed up. The systematic reviewers described this trial as ‘fair quality’. Factors affecting its validity were a high attrition rate between randomisation and screening; verification bias, as only women with positive cytology received colposcopy; and unequal crossover between study arms. In a subsample of 58,076 women aged between 30–60 years with linkage to registry data, followed up for an average of 3.3 years, the relative rate of CIN3+ in the HPV-triaged-by-cytology group compared with the cytology-
alone group was group was 1.44 (95% confidence interval (CI) 1.01 to 2.05). Among women with a negative screening result, the relative rate of subsequent CIN3+ in the HPV-triaged-by-cytology group compared with the cytology-alone group was 0.28 (95% CI 0.04 to 1.17). The study authors concluded that primary HPV testing followed by conventional cytology triage of positive results was more sensitive than conventional cytology in detecting CIN3+ lesions. Specificity for the detection of CIN2+ was 99.2% (95% CI 99.1% to 99.3%) in the HPV-triaged-by-cytology group and 99.1% (95% CI 99.0% to 99.2%) in the cytology-alone group. Generalisability of these findings to the Scottish context is lessened by the older population, different comparator and limited outcome data for CIN2+.

Other studies on the use of HPV testing in primary screening either examined co-testing with HPV and cytology, or stand-alone HPV testing. These are included as they provide additional evidence on the performance of HPV testing in primary screening compared with cytology. Results are reported from a 2006 meta-analysis by Cuzick et al., and recent primary studies. Earlier health technology assessments (HTAs) from the United Kingdom (UK), Australia and Belgium are now considerably out-of-date; and are not described in this evidence note.

Cuzick et al. in 2008 (updating the meta-analysis by Arbyn et al. from 2006) examined the absolute accuracy of stand-alone HPV testing using HC2 in eight studies conducted in Europe and the United States of America (USA). The pooled estimate of sensitivity of HC2 for the detection of CIN2+ was 98.1% (95% CI 96.8% to 99.4%; heterogeneity p=0.4). The corresponding estimate of specificity was 91.7% (95% CI 90.3% to 93.1%; heterogeneity p<0.001). This meta-analysis also reported on the relative accuracy of HC2 compared with conventional cytology or LBC using the ‘atypical squamous cells—undetermined significance’ or worse (ASC–US+) threshold on the Bethesda (2001) reporting system from 21 studies worldwide. Overall HC2 was 33% more sensitive (95% CI 20% to 47%) and 6% less specific (95% CI 2% to 8%) than cytology for the detection of CIN2+. A narrative synthesis of longitudinal studies on duration of disease-free survival led the authors to conclude that HPV testing allowed the screening interval to be safely extended to at least 6 years.

Monsonego et al. reported in 2011 on the French APTIMA® Screening Evaluation (FASE), of a three-way comparison among AHPV, HC2 and LBC as the single primary screening test, using a split-sample design in 4,429 women aged 20–65 years. ASC–US+ was the cut-off for LBC. All women positive on at least one screening test received colposcopy and biopsy; as did 14% of women with negative results on all three tests. Accuracy data, adjusted for verification bias, are presented in Table 1. The two HPV tests were substantially more sensitive than LBC at this threshold; whereas specificity of HC2 was slightly lower than both AHPV and LBC. These differences were particularly pronounced at younger ages (20–29 years).

Ronco et al. reported in 2010 on an Italian RCT, the second phase of which compared a single primary HPV test using HC2 with conventional cytology in 35,471 women aged 25–60 years. Two rounds of screening took place with an interval of 3 years. In women aged 35–60 years at the first round of screening, relative detection of CIN2+ in the HPV group compared with the cytology group was 2.13 (95% CI 1.50 to 3.03). At the second round of screening in this age group, relative detection of CIN2+ was 0.30 (95% CI 0.11 to 0.81) in the HPV group compared with the cytology group. In women aged 25–34 years at the first round of screening, relative detection of CIN2+ in the HPV group compared with the cytology group was 4.50 (95% CI 2.92 to 6.93). At the second round of screening in this age group, relative detection of CIN2+ was 0.40 (95% CI 0.17 to 0.95) in the HPV group compared with the cytology group. The authors concluded that HPV testing was more effective than cytology in preventing invasive cervical cancer, by detecting persistent high-grade lesions earlier and providing a longer low-risk period; but HPV screening in younger women led to over-diagnosis of regressive CIN2. They recommended that for women aged 35 years or older, HPV testing should be used for primary screening at prolonged intervals, with cytology reserved for triage of HPV-positive women.

Kitchener et al. reported in 2011 on the ARTISTIC trial of 8,873 UK women aged 20–64 years screened using LBC and HPV testing with HC2. Over 6-year follow up, the cumulative CIN2+ incidence in women negative for HPV at baseline, including disease found at baseline, was 0.87% (95% CI 0.70% to 1.06%). In contrast, the cumulative incidence of CIN2+ in women with negative baseline cytology, including disease found at baseline, was 1.41% (95% CI 1.19% to 1.65%). Cumulative CIN2+ incidence over three rounds of screening following a negative HPV test was similar to that over two rounds following a negative cytology test, leading the authors to conclude that primary HPV testing would allow screening intervals to be safely extended to 6 years.
Katki et al. reported in 2011 on a USA epidemiological study of 331,818 women aged 30 years or older enrolled in a 3-yearly screening programme of co-testing by conventional cytology and HPV testing using HC2 with Kaiser Permanente. Over 5-years follow up, the cumulative incidence of cervical cancer in women negative by HPV testing at baseline, including disease found at baseline, was 3.8 per 100,000 women per year. In contrast, the cumulative incidence of cervical cancer in women negative by cytology at baseline, including disease found at baseline, was 7.5 per 100,000 women per year. The authors concluded that testing for HPV as a sole primary test might be sufficiently sensitive in cervical cancer screening, with cytology reserved for positive HPV results.

Individual patient data from European and USA studies were combined in a 2006 meta-analysis by Cuzick et al. investigating the age-specific relative accuracy of stand-alone HPV testing using HC2 or PCR, and cytology. The authors reported that for the detection of CIN2+, sensitivity of HPV testing did not vary by age; whereas specificity increased with age. The authors concluded that HPV testing as a sole primary screening test was more sensitive and less specific than cytology at all ages; the difference in specificity being most pronounced among women younger than 35 years.

### Table 1 Estimates of absolute accuracy of HPV testing versus cytology for the detection of CIN2+ in primary screening for cervical cancer in Europe and US, by age

<table>
<thead>
<tr>
<th>Study</th>
<th>Population age</th>
<th>Test</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leinonen et al., 2009</td>
<td>24-34</td>
<td>HC2 triaged by cytology</td>
<td>Not available</td>
<td>98.2% (97.8% to 98.5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conventional cytology at Pap II</td>
<td>Not available</td>
<td>98.6% (98.2% to 98.9%)</td>
</tr>
<tr>
<td></td>
<td>35-44</td>
<td>HC2 triaged by cytology</td>
<td>Not available</td>
<td>99.0% (98.8% to 99.2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conventional cytology at Pap II</td>
<td>Not available</td>
<td>98.9% (98.6% to 99.1%)</td>
</tr>
<tr>
<td></td>
<td>45-54</td>
<td>HC2 triaged by cytology</td>
<td>Not available</td>
<td>99.6% (99.4% to 99.7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conventional cytology at Pap II</td>
<td>Not available</td>
<td>99.3% (99.1% to 99.4%)</td>
</tr>
<tr>
<td></td>
<td>55+</td>
<td>HC2 triaged by cytology</td>
<td>Not available</td>
<td>99.6% (99.5% to 99.7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conventional cytology at Pap II</td>
<td>Not available</td>
<td>99.5% (99.3% to 99.6%)</td>
</tr>
<tr>
<td>Monsonego et al., 2011</td>
<td>20-29</td>
<td>APTIMA®</td>
<td>99.7% (95.0% to 100%)</td>
<td>87.4% (85.4% to 89.4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HC2</td>
<td>99.7% (95.0% to 100%)</td>
<td>79.1% (76.7% to 81.6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LBC at ASC–US</td>
<td>67.7% (52.0% to 83.4%)</td>
<td>88.4% (86.5% to 90.3%)</td>
</tr>
<tr>
<td></td>
<td>30-65</td>
<td>APTIMA®</td>
<td>87.7% (79.2% to 96.2%)</td>
<td>93.2% (92.4% to 94.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HC2</td>
<td>95.0% (88.5% to 100%)</td>
<td>88.8% (87.7% to 89.9%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LBC at ASC–US</td>
<td>69.7% (58.4% to 81.0%)</td>
<td>93.1% (92.2% to 94.0%)</td>
</tr>
</tbody>
</table>
Screening interval

Dillner et al. reported in 2008 on the cumulative incidence of CIN3+ following a negative baseline HPV or conventional cytology test, using pooled data from 24,295 women enrolled in seven screening studies in six European countries, who had at least one cytology or histopathology follow-up test. The individual programmes varied in infrastructure and screening intensity, and mainly focussed on women older than 30 years. Six years after a negative baseline test, the cumulative incidence of CIN3+ was significantly lower among women negative for HPV (0.27%; 95% CI 0.12% to 0.45%) than among women with negative cytology (0.97%; 95% CI 0.53% to 1.38%). The low cumulative incidence of CIN3+ among women negative for HPV at baseline led the authors to conclude that a 6-yearly HPV screening strategy was safe and effective.

Longitudinal results from the HART study, comparing HPV testing using HC2 with conventional cytology in 8,735 UK women aged 30–60 years, were reported in 2010 by Mesher et al. The risk of developing CIN2+ 1, 3, 5 and 8 years after a negative baseline HPV test result, including disease found at baseline, was 0.09%, 0.12%, 0.23% and 0.61%, respectively. The equivalent results following negative baseline cytology were 0.21%, 0.28%, 0.48% and 1.04%, respectively. The authors concluded that HPV testing offered greater protection against CIN2+ than conventional cytology, and would allow the screening interval to be safely extended to at least 5 years.

Vaccination status

No evidence was found on the clinical effectiveness of primary HPV testing followed by cytology triage of positive results in screening of vaccinated women.

Self collection of cervical samples

The foregoing literature relates to cervical samples obtained by healthcare professionals. Good agreement has been found between results from self-collected and professionally-obtained samples. HPV self-testing may be potentially useful in groups poorly reached by the current screening programme.

Safety

The higher sensitivity of HPV testing compared with cytological testing means that more women who could otherwise go on to develop cervical cancer will be identified, thus improving safety. HPV testing followed by conventional cytology triage of positive results is also highly specific, avoiding the excess of ‘false positive’ results due to transient HPV infections and pre-clinical disease which occur with stand-alone HPV testing. A positive HPV result appears to be more stigmatising than a positive smear. Excisional procedures to treat CIN increase the risk of pregnancy-related morbidity.

Cost effectiveness

Accetta et al. reported in 2010 on an Italian cost-effectiveness study, in which a Markov model was developed to examine 18 preventive strategies in relation to lifetime risk of cervical cancer in women aged 25–65 years. The strategies were defined by vaccination (yes/no), primary screening test (none/conventional cytology/HPV), triage test (none/HPV/conventional cytology), and screening frequency (3 years/5 years). Baseline parameter values were obtained from published data. Age- and HPV-type-specific transition probabilities between health states of healthy, low-risk HPV infection, high-risk HPV 16/18 infection, high-risk HPV non-16/18 infection, low-grade precancerous lesions, high-grade precancerous lesions, local cancer, regional cancer and distant cancer were based on published data and expert opinion. The probability of death was based on the Tuscan Cancer Registry and Italian life tables. Costs were determined from the Tuscan region’s cervical screening programme and interviews with healthcare professionals in local hospitals using an activity-based costing method for the index year 2006. Costs and benefits were discounted at 3% per year. One-way sensitivity analysis was performed. The authors concluded that 5-yearly primary HPV testing using HC2, with cytology triage of positive results, was more effective and less costly than the current screening policy of 3-yearly conventional cytology. For unvaccinated women, the incremental cost-effectiveness ratio (ICER) was €5,753 (approximately £4,900 in November 2011) per quality-adjusted life expectancy (QALE). Vaccination at age 11 years followed by the same screening strategy was also cost effective (ICER €23,951 (approximately £21,000 in November 2011) per QALE).

Vijayaraghavan et al. reported in 2010 on a Markov model to examine the cost utility of HPV testing in primary cervical screening of women aged 30 years and older in Quebec. Women younger than 30 years were assumed to be screened using conventional cytology. The strategies were defined by primary screening test (none/conventional cytology/HPV/co-testing), triage test (none/HPV/conventional cytology), and screening frequency (1 year/3 years). HPV incidence was estimated from HPV prevalence in Quebec. Test performance was obtained from the
Canadian Cervical Cancer Screening Trial. Age-specific utilities were obtained from the WHO-CHOICE program. A healthcare-payer perspective was used. Costs and outcomes were discounted at 5% per year. A strategy of 3-yearly HPV testing with cytology triage of positive results had an ICER of Canadian $8,358 (approximately £5,100 in November 2011) per quality-adjusted life year (QALY) compared with 3-yearly conventional cytology. One-way sensitivity analysis showed ICERs were most affected by changes to the risk of progression from HPV infection to CIN, cervical cancer progression rates and the CIN1 regression rate.

These economic evaluations suggest that primary HPV testing followed by conventional cytology triage of positive results, with a 5-year screening interval, may be cost effective compared with 3-yearly conventional cytology. However, generalisability to the Scottish context is uncertain due to differences in health systems, populations and comparators.

Conclusion

No direct evidence was found on whether HPV testing, followed by LBC triage of positive results, is clinically effective in primary screening for cervical cancer compared with current Scottish practice of 3-yearly screening using LBC. Results have been reported on the closest-matching alternative intervention and comparator screening protocols. This evidence showed that HPV testing with HC2, followed by conventional cytology triage of positive results, is highly sensitive and highly specific in primary screening for cervical cancer. HPV testing triaged by conventional cytology is more sensitive than conventional cytology alone. In women older than 35 years, HPV testing triaged by conventional cytology is more specific than conventional cytology alone. There is a lack of evidence on specificity of HPV testing triaged by cytology applicable to women aged 20–35 years.

The evidence suggests that primary HPV testing allows the screening interval to be safely extended to at least 6 years. A 5-year screening interval for HPV testing triaged by cytology may be cost effective compared with conventional cytology.

Any proposal to introduce HPV testing in the Scottish Cervical Screening Programme may require different management strategies to be identified for cohorts defined by vaccination status and age.

Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.

The evidence note process has been assessed and no adverse impact across any of these groups is expected. The completed equality and diversity checklist is available on www.healthcareimprovementscotland.org

About evidence notes

For further information about the evidence note process, see www.healthcareimprovementscotland.org

To propose a topic for an evidence note, email evidencenotes.HCIS@nhs.net

References can be accessed via the internet (where addresses are provided), via the NHS Knowledge Network http://www.knowledge.scot.nhs.uk, or by contacting your local library and information service.

Acknowledgements

Healthcare Improvement Scotland would like to acknowledge the helpful contribution of the following, who gave advice on the content of this evidence note:

- Breast and Cervical Screening National Advisory Group HPV reference group
- Healthcare Improvement Scotland development team
  - Joanne Abbotts, Lead Author/Health Services Researcher
  - Heather McIntosh, Project Lead/Health Services Researcher
  - Jenny Harbour, Information Scientist
  - Susan Downie, Medical Writer
  - Doreen Pedlar, Project Co-ordinator
  - Marina Logan, Team Support Administrator

© Healthcare Improvement Scotland 2012
ISBN 1-84404-931-0
References


