Canadian Agency for Drugs and Technologies in Health

HTA

HEALTH TECHNOLOGY INQUIRY SERVICE (HTIS)

Title: Human Papillomavirus Screening for Cervical Cancer: Use as a Primary Screening Test

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Context and policy issues:

In Canada, it was estimated that 1350 new cases of cervical cancer would be diagnosed and there would be 390 deaths from this disease in 2007.[1] Human papillomavirus (HPV) infection can be found in most cases of cervical cancer.[2] It has been estimated that between 90.7% and 96.6% of cervical cancer cases are associated with HPV infection.[2] There are particular subtypes of HPV that are detected more frequently and that can be classified as high-risk, possibly high-risk or low-risk.[2] Many HPV infections are transient and can regress.[2,3] There are three levels of positive cytology results: atypical squamous cells of undetermined significance (ASCUS+), low-grade squamous intra-epithelial lesions (LSIL+) and high-grade squamous intra-epithelial lesions (HSIL+).[3] Cervical intraepithelial neoplasia (CIN) is used to describe lesions that are confirmed histologically and screening tests should be able to detect the higher grades (CIN2+ and CIN3+).[3]

Screening for cervical cancer is traditionally done with conventional cytology, using a Pap smear.[2] The sample is collected by scraping cells from the cervix and those cells are then smeared on a glass slide for analysis.[2] If ASCUS, LSIL or HSIL are detected, follow-up testing should be conducted by biopsy or colposcopy.[2] Biopsy is done if a high grade cancer is suspected and colposcopy is done for abnormal smears that may be cancer.[2] Liquid-based cytology (LBC) is similar to the Pap smear; sample collection is the same but the sample is transferred to a liquid media for analysis.[2]

The detection of HPV within cervical cells can be done using molecular techniques[2] and is another method to screen for cervical cancer.[4] The Hybrid Capture 2 (HC2) test and polymerase chain reaction (PCR) are both methods that can be used to detect HPV.[2,4] In Canada, HPV testing is only indicated for women over the age of 30 years with ASCUS as a

triage for colposcopy.[2] HPV testing may not be useful in younger women, as HPV infection is often transient in women under the age of 30 years.[2] Research regarding the detection of HPV infection as a screening test is being conducted and it will be necessary to review the available evidence to determine whether HPV testing can be used as the primary test for cervical cancer screening.

Research question:

1. What is the clinical effectiveness of HPV testing as a primary stand-alone test for cervical cancer screening?

Methods:

A limited literature search was conducted on key health technology assessment resources, including Pre-Medline, Medline, Embase, Biosis, Pubmed, the Cochrane Library (Issue 1, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2003 and February 2008, except for guideline articles published between 2006 and February 2008. All the results were limited to English language publications only. Filters were applied to limit the retrieval to systematic reviews/HTA, guideline studies, and randomized controlled trial studies.

Summary of findings:

Studies were included that examined the use of HPV as a primary screening test. Studies that used HPV testing in conjunction with cytology were excluded. There was one Health Technology Assessment (HTA) and five systematic reviews (SRs) and/or meta-analyses identified on this topic. In addition, two guidelines and four randomized controlled trials (RCTs) were identified.

Health technology assessments

A technology report from this agency [The Canadian Agency for Drugs and Technologies in Health; CADTH (formerly the Canadian Coordinating Office for Health Technology Assessment; CCOHTA) was published in 2003 on LBC and HPV testing for cervical cancer screening.[5] This study investigated the diagnostic accuracy of HPV testing for detection of precancerous or malignant cervical lesions. Studies were included that screened women using LBC or HPV testing, and conventional cytology with Pap smears was used as the control. Outcome measures were sensitivity and specificity. There were 30 reports identified that studied HPV testing versus cytology; 22 were unique trials and 12 of these studied the use of HPV testing as a primary screening test. Of the 12 trials, 4 compared combined HPV testing and Pap smears to Pap smears and only 6 controlled for verification bias. Histology for CIN2/3 was used as the reference standard in all trials. The sensitivity of HPV testing was higher compared to Pap smears, but the specificity was lower (Table 1). An important limitation to studies included in this HTA is the lack of control for verification bias as histological testing was not done on all subjects in the trials. As a result, sensitivity and specificity may have been overestimated. Overall, this HTA reports a higher sensitivity of HPV testing compared to Pap smears but a lower specificity.

Systematic reviews and meta-analyses

Data from the three meta-analyses [3,6,7] as well as the health technology assessment described above [5], are reported in Table 1.

A recent meta-analysis (2007) was published examining the accuracy of HPV testing for cervical cancer screening.[6] Studies were included that examined women from 18 years to 70 years of age not currently being followed for an abnormal cytology result, were RCTs or non-RCTs comparing HPV testing to cytological screening, and used colposcopy or biopsy as the gold standard for positive test results. Twenty-five studies were included and only one was an RCT; the remaining were cross-sectional studies (n = 23) and one longitudinal study. In all studies, women were recruited from the general population and sample sizes ranged from 813 to 36,938. There were variations between the studies on controlling for verification bias; 4 studies performed the gold standard on all participants, 8 performed the gold standard on all positive results and a random sample of negative results, 12 performed the gold standard on all positive results and one study only performed the gold standard on the positive results obtained by Pap smears and not on HPV positive results. The pooled sensitivity was highest for HPV testing using the HC2 test and lowest for cytology with a LSIL threshold (Table 1). There was variation between the studies for sensitivity and specificity of all the tests. Limitations to this meta-analysis include the verification bias present in some of the studies which would result in inaccurate sensitivity results. However, the authors found that verification bias did not affect the sensitivity of HPV testing using the HC2 test (80.8 – 97.8% controlling for verification bias versus 88.4% - 100% not controlling for verification bias). Specificity ratios are not affected by verification bias. Overall, the authors concluded that HPV testing has a higher sensitivity compared to cytology. It was suggested that longitudinal studies are needed to determine if HPV testing will result in a reduction in cervical cancer incidence if used as a primary screening test.

A meta-analysis from the Belgian Health Care Knowledge Centre was published in 2006.[3] Limited information was provided regarding methodology. A meta-analysis was conducted on the accuracy of HPV testing compared to cytology for identifying women with intraepithelial neoplasia. They identified 24 studies that screened women using HPV testing and Pap smears and pooled the results. Sensitivity of HPV testing by both the HC2 test and PCR was higher than cytology (Table 1) but the specificity was lower. The area under the curve (AUC) of the receiver operating characteristic (ROC) plot was 96.1% (95% CI: 94.2% – 97.5%). An AUC closer to 100% indicates a perfect test.[8] The authors concluded that HPV testing is more sensitive than cytology, but less specific and more research is necessary to better define these values.

A summary and update of previous meta-analyses was published in 2006.[7] The previous meta-analyses that are summarized focused on triage of women and follow-up after treatment. The update to this report is a meta-analysis on HPV testing as primary screening for cervical cancer. The majority of studies that were included in this meta-analysis were cross-sectional studies and all were in asymptomatic women (n = 24). Verification bias was controlled for in some of the studies by selecting a random sample of screen negative women for colposcopy (n = 8), but most only referred screen positive women for colposcopy (n = 10). The remaining six studies referred all women for colposcopy. Pooled sensitivities and specificities were reported for HPV testing (Table 1) but were not reported for the control cytology group. It was reported that 23% more cancers are detected with HPV testing compared to cytology but HPV testing is 6% less specific. The studies outside of North America and Europe had much lower sensitivities and specificities and therefore, pooled data is reported for all studies and also for the North

American and European studies alone. This study concluded that HPV testing may be useful for triage of women following atypical cytology results, but did not make any conclusions for HPV testing as the primary screening test. A limitation to this study is the fact that the pooled sensitivity and specificity of cytology was not reported making it difficult to compare cytology to HPV testing.

Table 1: Measures of accuracy of cervical cancer screening tests from meta-analyses

Study	Test	Sensitivity % (95% CI)	Specificity % (95% CI)	Sensitivity ratio (to cytology)	Specificity ratio (to cytology)
Noorani et al, 2003 [5]	HPV	68 – 100	16 – 97	NR	NR
	cytology	20 – 89	87 – 99	NR	NR
Koliopoulos et al, 2007[6]	HPV (HC2)	90 (86.3 – 93.7)	86.5 (83.1 – 89.8)	ASCUS:1.25 (1.20 – 1.29) LSIL: 1.38 (1.30 – 1.47)	ASCUS: 0.97 (0.96 – 0.98) LSIL: 0.89 (0.87 – 0.90)
	HPV (PCR)	80.9 (70.0 – 91.7)	94.7 (92.5 – 96.9)	NR	NR
	Cytology (ASCUS)	72.7 (63.9 – 81.5)	91.9 (90.2 – 93.6)	NR	NR
	Cytology (LSIL)	61.6 (48.0 – 75.2)	96.0 (94.8 – 97.2)	NR	NR
Hulstaert et al, 2006[3]	HPV (HC2)	89.3 (85.2 – 93.4	87.8 (85.5 – 90.0)	1.23 (1.13 – 1.23)	0.94 (0.92 – 0.96)
	HPV (PCR)	80.9 (70.0 – 91.7)	94.7 (92.5 – 96.9)	1.25 (0.95 – 1.63)	NR
Arbyn et al, 2006[7]	HPV (HC2)	CIN2+: 89.5 (85.1 – 93.1) (all studies) 97.9 (95.9 – 99.9) (NA and European studies) CIN3+: 89.0 (82.5 – 95.5)	CIN2+: 87.5 (85.0 – 89.9) (all studies) 91.3 (89.5 – 93.1) (NA and European studies) CIN3+: 90.8 (88.4 – 93.2)	NR	NR
	HPV (PCR)	CIN2+: 80.9 (70.0 – 91.7)	CIN2+: 94.7 (92.5 – 96.9)	NR	NR

HPV = human papillomavirus
CIN = cervical intraepithelial neoplasia
LSIL = low-grade squamous intra-epithelial lesions
ASCUS = atypical squamous cells of undetermined significance
PCR = polymerase chain reaction
NA = North American
NR = not reported

A systematic review published in 2003 examined the effectiveness of HPV testing for cervical cancer screening.[9] There were two articles included in this review. The first compared the HC2 test to cytology in 7932 women and only women with a positive result on cytology were referred

to colposcopy. Women with a positive result with HC2 testing were referred for cytology and further HC2 testing. The sensitivity was 100% for HC2 testing, 87.9% for LBC and 66.1% for Pap smears. The specificity was 87.3% for HC2 testing, 93.1% for LBC and 95.3% for Pap smears. For women aged 30 years and older, the sensitivity and specificity was 100% and 88.4% for HC2 testing, 84.4% and 94.8% for LBC and 57.7% and 95.6% for Pap smears. The second study included 4075 women. Sensitivity was 90.8% for HC2 testing, which was the highest of all the screening tests and specificity was 72.6%, which was the lowest of all the screening tests. The sensitivity and specificity of the other screening tests (HPV testing by PCR and LBC) was not reported in the systematic review. This report concluded that although the sensitivity of HPV testing is high, evidence is limited to determine whether HPV testing is more advantageous than cytology screening.

A systematic review on cervical cancer screening was conducted by Cancer Care Ontario.[4] The Cervical Screening Guidelines Development Committee reviewed the evidence which included SRs, HTAs and guidelines comparing screening tests. There were only two reports identified that compared primary HPV testing to conventional cytology. One was the HTA reported above from CCOHTA and the other was an older assessment from the NHS HTA program. The NHS HTA reported a higher sensitivity but a lower specificity with HPV testing compared to cytology. Overall, this SR found that the evidence does not recommend HPV testing as a primary screening test, but concluded that it may be useful in the future for cervical cancer screening.

Randomized controlled trials

Table 2 summarizes the sensitivity and specificity data from the first three RCTs.[10-12] The fourth RCT [13] did not report sensitivity and specificity.

An RCT from the Canadian Cervical Cancer Screening Trial Study Group was published in 2007.[10] The objective was to determine if HPV testing was more effective than Pap testing for cervical cancer screening. There were 10,154 women randomly assigned at a 1:1 ratio to the Pap group or the HPV group. The Pap group received the Pap test first followed by HPV testing (on the same day) and this order was reversed for the HPV group. HPV testing was done using the HC2 test. Colposcopy was offered to women who were positive on either the Pap test or the HPV test. Colposcopy was also offered to a percentage of the women who had a negative index test to control for verification bias. The study concluded that HPV testing is more sensitive but less specific than Pap testing.

An RCT from the New Technologies for Cervical Cancer Working Group was published in 2006.[11] The objective of this study was to compare HPV testing with conventional cytology. Women aged 25 years to 60 years were included in this trial which randomized women 1:1 to the conventional arm or the experimental arm. The conventional arm were screened using conventional cytology (Pap) and were referred to colposcopy if LSIL or higher was detected. Women in the experimental arm were screened using LBC and HPV testing (HC2 assay) in the first phase and HPV only in the second phase. Women were referred for colposcopy if HPV test results were positive or if LBC results were positive. There were 16,658 women in the conventional arm and 16,706 women in the experimental arm. Results were reported for only the first phase of the study. Overall, the sensitivity was higher for HPV than LBC. This study used different HPV concentration cutoffs for diagnosis of HPV infection and referral for colposcopy. Sensitivity and specificity results are therefore reported for a cutoff of 1 pg/ml and a cutoff of 2 pg/ml. Results from the second phase of this trial which is ongoing will further address the use of HPV testing alone for cervical cancer screening. A limitation to this study is

the fact that colposcopies were not done on every woman screened, so the results are subject to verification bias.

Primary HPV testing was assessed in a 2005 RCT.[12] Participants were randomized 1:1 to the HPV group or the conventional cytology (Pap) group. The HPV group received HPV screening using the HC2 test in addition to cytology. On the day of testing, participants in the HPV group had two samples taken, one for HPV testing and one for cytology. The cytology sample was stored if the HPV test result came back negative. If the HPV test was positive, cytology was conducted using the stored sample. Colposcopy was carried out in patients with positive cytology results. There were 4653 women in the HPV group and 4245 received HPV testing primarily (the remaining 408 did not receive HPV testing; random allocation was not followed and they received cytology instead); 395 of these women had positive HPV test results and their cytology sample was then screened. There were 4650 women in the conventional cytology group. The relative risk (RR) of referral for colposcopy was higher in the HPV group compared to the cytology group (RR 1.51; 95% CI 1.03 – 2.22). Sensitivity was not reported and the specificity was lower in the HPV group compared to the cytology group. The authors concluded that HPV testing should only be used as the primary screening test if cytologists are unavailable.

Another RCT compared cervical cancer screening tests and reported on detection rates.[13] There were 497 villages in India involved in the study which included women aged 30 years to 59 years with no previous history of cervical cancer. Women were randomized to a control group (n = 33,696), a HPV group (n = 36,938), a cytology group (n = 35,193) and a visual inspection group (n = 36,874). The control group received health education on cervical cancer, and 5.8% (1946) of participants in the control group requested screening following the education. They received cytology and 15 were detected with CIN2/3 and 41 were detected with cancer. The detection rate of CIN 2/3 was 0.7% in the visual inspection group, 1.0% in the cytology group and 0.9% in the HPV group. The cancer detection rate was 0.3% in the visual inspection group, 0.3% in the cytology group, 0.2% in the HPV group and 0.2% in the control group. The authors concluded that HPV testing did not result in an improvement in detection rates.

Table 2: Measures of accuracy of cervical cancer screening tests from RCTs

Study	Test	Sensitivity % (95% CI)	Specificity % (95% CI)	Sensitivity ratio (to cytology)	Specificity ratio (to cytology)
Mayrand et al, 2007[10]	HPV (HC2)	94.6 (84.2 – 100.0) (p = 0.01)	94.1 (93.4 – 94.8)	NR	NR
	Pap	55.4 (33.6 – 77.2)	96.8 (96.3 – 97.3) (p < 0.001)	NR	NR
Ronco et al, 2006[11]	HPV (HC2) (≥1 pg/ml)	CIN2+: 97.3 (90.7 – 99.7) CIN3+ :97.4 (86.5 – 99.9)	CIN2+: 93.2 (92.8 – 93.6) CIN3+: 93.0 (92.6 – 93.4)	CIN2+: 1.43 (1.00 – 2.04) CIN3+: 1.22 (0.76 – 1.96)	NR
	HPV (HC2) (≥2 pg/ml)	CIN2+: 96.0 (88.8 – 99.2) CIN3+: 94.9 (82.7 – 99.4)	CIN2+: 94.9 (94.5 – 95.2) CIN3+: 94.7 (94.3 – 95.0)	CIN2+: 1.41 (0.98 – 2.01) CIN3+: 1.19 (0.74 – 1.92)	NR
	LBC	CIN2+: 74.0 (62.4 – 83.6) CIN3+: 81.6 (65.7 – 92.3)	CIN2+: 94.8 (94.5 – 95.2) CIN3+: 94.7 (94.4 – 95.0)	CIN2+: 1.06 (0.72 – 1.55) CIN3+:1.00 (0.61 – 1.64)	NR
Kotaniemi-Talonen et al, 2005 [12]	HPV (HC2)	NR	CIN 2+: 91.7 (90.9 – 92.5) CIN 3+: 91.5 (90.7 – 92.3)	NR	NR
	cytology	NR	CIN 2+: 99.3 (99.0 – 99.5) CIN 3+: 99.2 (98.9 – 99.4)	NR	NR

HPV = human papillomavirus
LBC = liquid based cytology
CIN = cervical intraepithelial neoplasia
NR = not reported

Guidelines

In 2007, the Canadian Consensus Guidelines on Human Papillomavirus were published discussing the role of HPV testing for screening for cervical cancer.[2] The Canadian Task Force on Preventive Health Care ranking was used to rate the quality of the evidence. HPV testing is currently only used for triage of women over the age of 30 years who have had ASCUS to decide whether colposcopy should be done. These guidelines recommended:

1. HPV testing for women 30 years and older with ASCUS; to be used as an adjunct to cervical cytology. Grade 1A (evidence obtained from at least one RCT; good evidence for the recommendation)
2. HPV testing should not be done in women under the age of 30 years. Grade 1A
3. HPV testing should not be done as a triage in women with LSIL, HSIL and squamous cell carcinoma. Grade 1A[2]

These guidelines state that HPV testing is not used for cervical cancer screening in Canada, but it is a potential option.

The American Cancer Society 2006 Guidelines for early cancer detection [14] recommended HPV testing in conjunction with cytology. There were no recommendations regarding HPV testing as a primary screening test.

Limitations

Of the four RCTs identified, only one was from Canada.[10] The others were from India,[13] Finland[12] and Italy[13] and therefore it is unclear whether these results would be generalizable to the Canadian population. In addition, only the Canadian study controlled for verification bias. In the other three RCTs, only participants with positive screening results underwent the reference test (colposcopy) and therefore, sensitivity is likely to be overestimated in these studies. Furthermore, some of the studies included in the systematic reviews did not control for verification. Also, many of the studies included in the meta-analyses were observational studies, which do not control for potential selection bias. There is currently no long-term data for how HPV testing compares with conventional cytology for the reduction of cervical cancer.

Conclusions and implications for decision or policy making:

The evidence suggests that HPV testing is more sensitive than conventional cytology for cervical cancer screening; however, it is also less specific. In the meta-analyses, the pooled sensitivity of HPV testing ranged from 68% to 100% and the pooled specificity ranged from 16% to 97%. For cytology, the pooled sensitivity ranged from 20% to 89% and the specificity ranged from 87% - 99%. In the RCTs, the sensitivity ranged from 94.6% to 97.4% for HPV testing and 55.4% to 81.6% for cytology. Specificity ranged from 91.5% to 94.9% for HPV testing and 94.7% to 99.3% for cytology in the RCTs. The lower specificity of HPV testing would result in an increase in false positive results and unnecessary referrals for colposcopy. The guidelines that were identified from the past two years do not recommend using HPV testing as a primary test for cervical cancer screening.

The criteria for an effective screening test include simplicity (the test must be easy), acceptability (to the patients), accuracy, cost, precision, sensitivity and specificity.[15] Based on the evidence, HPV testing appears to meet most of the criteria for an effective screening test. HPV testing is likely more costly than cytology and therefore, this may be a consideration when deciding whether to use HPV testing as the primary screening test. In addition, some HPV infections are transient [2,6] so the usefulness of HPV testing is unclear in women under 30 years of age when the HPV infection is likely to resolve on its own.[2,3] It is unclear from the studies that were identified whether HPV testing will result in a reduction in the mortality rate due to cervical cancer. Long-term studies will be necessary to determine if HPV testing has any benefit on mortality compared with conventional cytology.

Prepared by:

Lesley Dunfield, PhD, Interim Manager
Karen Cimon, Research Assistant
Emmanuel Nkansah, MLS, MA, Information Specialist
Health Technology Inquiry Service
Email: htis@cadth.ca
Tel: 1-866-898-8439

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