

# HPV Testing for Primary Cervical Cancer Screening

## Key Messages

- Human papillomavirus (HPV) is the major risk factor for the development of cervical cancer; HPV testing directly detects the presence of the virus.
- The CADTH review found that HPV tests are better at detecting cancer precursors than cytology but less effective at identifying those who may not have cancer despite having HPV. Screening with HPV tests is also associated with increased referral to colposcopy compared with cytology.
- The CADTH review found that switching the primary test from cytology to HPV testing and decreasing the screening frequency decreased costs, with limited harms.
- Screening involves balancing the benefits of disease detection with the harms and burdens of screening participation, including false-positives and overdiagnosis.
- A switch to HPV testing would be a large operational and cultural shift for clinicians, patients, and laboratories. Successful implementation would require appropriate planning, funding, and coordination.



## INCLUDED IN THIS SUMMARY

- A brief background on cervical cancer and current modalities for screening for cervical cancer in Canada
- Evidence highlights from the clinical, economic, ethical, and implementation findings and patient perspectives of the CADTH review

This summary is based on a Health Technology Assessment conducted by CADTH.

### Cervical Cancer

Worldwide, cervical cancer is one of the most frequently diagnosed cancers. In 2017, it is estimated that there were 1,550 cervical cancer cases diagnosed and 380 deaths related to cervical cancer in Canada. The incidence of cervical cancer has been decreasing in the past three decades, largely due to routine screening with cytology.

Cervical cancer occurs when cancerous cells form a tumour on the cervix. When the cancerous cells spread beyond the surface, it is classified as invasive. Human papillomavirus (HPV) is the major risk factor for the development of cervical cancer, with 99% of cervical cancers being associated with HPV. HPV is one of the most common sexually transmitted infections (STIs) in the world and approximately three out of every four sexually active Canadians will have at least one HPV infection at some point in their lives. The majority of these HPV infections will resolve on their own within one to two years, without causing any issues.

Approximately 40 HPV genotypes are known to be involved in genital HPV infections, 13 of which have been designated as the highest-risk HPV types because of their strong oncogenic potential. HPV types 16, 18, 31, 33, 45, 52, and 58 are estimated to account for more than 90% of invasive cervical cancers. Infection with HPV can lead to the development of a variety of cancers – including cervical, vaginal, and penile – as well as cancer of the anus, mouth, and throat. Most of the HPV infections that are associated with the development of these cancers can now potentially be prevented with vaccination.

### Cancer Screening

Screening tests are used to identify those people at risk of developing cancer. Cervical cancer screening aims to reduce the risk of disease and associated mortality by detecting and treating precursor lesions before they progress to cervical cancer. In Canada, data shows that routine screening with cytology improves survival from cervical cancer. The lifetime risk of dying from the disease is currently one in 100 for those who do not undergo screening with cytology and one in 500 for those who do.

The screening programs and approaches that have been adopted in Canada vary by province and most are based on cytology screening. Existing guidelines recommend that cervical cancer screening with cytology be done every two to three years, starting at age 21 or 25 through to ages 65 to 70, depending on the jurisdiction.

With positive screening tests (abnormal cytology results), individuals are suspected as having precancerous or more severe lesions. A confirmatory exam may be conducted whereby a clinician directly examines the cervix through colposcopy; a biopsy may then be conducted, if indicated. Any confirmed precancerous or cancerous lesions are referred for further treatment.

## Cytology Testing

In the context of cervical cancer screening, cytology testing is used to identify the presence of precancerous cell changes in the cervix. There are two types of cytology: conventional (also known as the Papanicolaou [Pap] test) and liquid-based. Conventional cytology involves the collection of cells from the surface of the cervix, which are then spread on a slide and visually examined for abnormalities in a laboratory. For liquid-based cytology (LBC), cells are collected in liquid vials and are prepared semi-automatically in the laboratory and then examined. In contrast to conventional cytology samples, a single sample obtained for LBC can be used to perform multiple different tests.

Cytology testing can also be used in combination with other studies as a triage test, particularly HPV testing. When an abnormal result is detected with the cytology test, an HPV test may be used to identify the presence of cancer-causing strains of HPV before deciding whether follow-up testing with colposcopy is required.

## Human Papillomavirus Testing

HPV tests detect the presence of HPV DNA or ribonucleic acid in a sample of cervical cells, with a positive result indicating an HPV infection. Partial genotyping tests indicate whether HPV is present and, if so, whether high-risk variants of the virus are present in the sample. Full genotyping tests identify all the HPV strains present in the sample.

Unlike cytology testing, for which samples are collected solely by a health care provider, HPV-based tests can be collected either by a clinician or by the screening participants themselves; self-sampling can be useful to encourage screening participation in under- and never-screened populations. HPV tests can be used alone, administered at the same time as cytology testing (co-testing), or in combination with one or more triage tests.

HPV-based screening is expected to offer some benefits over cytology, such as higher sensitivity, the potential for increasing the time interval between screening visits, and the potential to initiate screening at an older age. With HPV testing, the screening interval may be extended to at least five years for those with a negative HPV test result, given findings of a lower risk of cervical cancer after a negative HPV test compared with a negative cytology test. Similarly, it is often suggested that primary HPV testing should not be used for participants younger than 30 years of age given the higher rate of transient HPV infections among those younger than 30.

Primary HPV screening has not been implemented in Canadian jurisdictions; however, a number of jurisdictions are currently considering, planning, or piloting primary HPV screening for their cervical cancer screening programs.

## What does the evidence say?

CADTH conducted a health technology assessment to inform policy decisions through a review of the evidence relating to clinical effectiveness and cost-effectiveness, patients' perspectives and experiences, ethical issues, and implementation issues regarding the use of HPV screening versus cytology-based primary cervical cancer screening programs. What follows are the highlights from the evidence found in the CADTH review.



### Bottom Line

HPV tests are found to be consistently more sensitive and less specific than cytology testing. Compared with cytology testing, HPV-based screening leads to higher rates of referral to colposcopy.

### Clinical Findings

Based on the evidence for the comparison between HPV tests and cytology, four systematic reviews and 20 primary studies were included in this review. Hybrid Capture 2 (HC2) was the most extensively studied HPV test and was found to be more sensitive and less specific than cytology, including conventional or LBC in most included studies. There is consistent evidence to show that other HPV tests were also more sensitive and less specific than cytology, including polymerase chain reaction-based tests, multiplex genotyping, and the Aptima, cobas, and Confidence HPV tests.

Overall, the review found a trade-off between the sensitivities and specificities of the triage strategies examined. Primary HPV testing with an HPV test and cytology co-testing seemed to have the highest sensitivity. Primary HPV testing followed by sequential genotyping and cytology seemed to have the highest specificity.

While there was limited evidence available to address harms and clinical utility, the evidence was consistent in demonstrating that primary high-risk HPV screening led to a statistically significantly increased detection of cervical intraepithelial neoplasia 3+. The evidence also showed that higher colposcopy referral rates were observed among those screened with HPV tests compared with cytology.

The evidence suggests that HPV testing as a stand-alone primary screening strategy or in co-testing should not be used for participants younger than 30 years of age. The higher rate of transient HPV infections among those younger than 30 years combined with the high sensitivity of HPV testing could lead to false-positives (i.e., HPV-positive test results in those without precancerous cervical lesions). This can lead to unnecessary worry for the patient, as well as unnecessary interventions, such as referral for a colposcopy for those without precancerous changes.



### Bottom Line

Switching the primary test from cytology to HPV testing and decreasing the screening frequency from three to five years could reduce the cost of cervical cancer screening in Canada and with limited harm.

### Economic Considerations

A decision-analytic hybrid model was developed to determine, from a health systems perspective, the lifetime cost-effectiveness associated with the following approaches to programmatic cervical cancer screening:

- primary cytology
- primary cytology with HPV triage for inconclusive cytology results
- primary HPV with cytology triage for HPV-positive results.

The main outcome was cost per quality-adjusted life-years (QALYs) gained.

In total, nine different screening strategies were assessed that varied in the screening interval (i.e., the starting age of screening and/or the frequency between screens [e.g., three or five

years]). The model did not compare between different commercial assays of the HPV tests nor the impact from the increasing practice of HPV genotyping to inform clinical management.

While more frequent screening (e.g., every year versus every three or five years) may improve the effectiveness of a screening program, the economic analysis found that this may also increase the burden for participants and health care providers, and costs for public health payers.

The economic evaluation found that switching the screening test from primary cytology to primary HPV testing with cytology triage and keeping all other characteristics of a screening program constant (e.g., interval, frequency) resulted in higher lifetime costs. However, switching the primary test from cytology to HPV testing and decreasing the screening frequency from five to three years could reduce the cost of cervical cancer screening in Canada with limited harm in terms of lifetime risk of developing cervical cancer.

Overall, there was little difference in QALYs and lifetime risk of cervical cancer between screening strategies. Regardless of the population age or vaccination status, the model found that primary HPV with cytology triage every five years from the ages of 30 to 69 was associated with the lowest costs and fewest QALYs.



## Patients' Perspectives and Experiences

A systematic review of the literature relevant to patients' experiences and perspectives with cervical cancer screening was conducted. A total of 117 primary studies were included in the review.

### Bottom Line

Some of the strongest patients' preferences would not be affected by a change in screening modality from cytology to HPV testing, as the potential for embarrassment, pain, and logistical inconvenience of both approaches is similar; however, learning of one's STI status can be daunting.

Several factors were identified that act alternately as incentives or disincentives to participating in cervical cancer screening: emotions, cultural and community attitudes and beliefs, understanding personal risk, logistics, relationships with health care providers, and knowledge. The review underscored the fact that many screening participants do not understand the link between HPV and cervical cancer, which can often lead to a misunderstanding about the nature and importance of HPV testing. As a result of this misunderstanding, many may underestimate their personal risks and decline to participate in screening.

According to the literature, some of the strongest patients' preferences would not be affected by a change in screening modality from cytology to HPV testing, as the potential for embarrassment, pain, and logistical inconvenience of both approaches is similar. However, a patient learning of their STI status through the results of HPV testing has been reported to be daunting, has led to associated problems of disclosure of that STI status to their sexual partner(s), and has provoked the fear of stigmatization.

The evidence suggests that, if cytology is replaced by HPV testing as the primary cervical cancer screening test in Canada, patient education that focuses on the etiology and risk factors of cervical cancer may improve participation rates. The importance of the relationship between patients and their health care providers will also continue to be important.



### Bottom Line

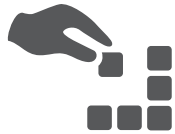
The balance of screening-related harms and benefits is affected by test characteristics and by the nature of the test. Any increase in harms should be weighed and justified by minimizing these harms and increasing the benefits.

### Ethical Considerations

A systematic review to determine the ethical and legal issues that have been identified for HPV as a primary cervical cancer screening test was performed.

Cancer screening involves balancing the benefits of disease detection with the harms and burdens of screening participation, false-positives, and overdiagnosis. This balance of harms and benefits is affected by test characteristics and by the nature of the test. Any increase in screening-related harms (e.g., potentially increased colposcopy referrals and increased false-positives) should be weighed and justified in a transparent manner by minimizing these harms and increasing the benefits (e.g., reduced colposcopy referrals and false-positives, and reduced cervical cancer mortality).

Decision-makers should be transparent about the basis for adopting or not adopting HPV testing as a primary screening method and should also ensure that necessary steps are taken to minimize harms. The balance of harms and benefits also depends on patients and providers following guidelines intended to delay screening start and extending the interval between screenings.



### Bottom Line

A switch to HPV testing would be a large operational and culture shift for clinicians, patients, and laboratories. Good planning, funding, and coordination would be needed for a successful implementation.

### Implementation Issues

To understand the issues associated with implementing HPV testing for primary cervical cancer screening, a literature search was conducted and targeted experts and stakeholders (laboratory, pathology, and cancer specialty sectors) were consulted.

A change to HPV-based screening would be a significant operational and culture shift for clinicians, patients, and laboratories. If a switch is made, good planning, funding, and coordination will be needed to ensure that implementation runs smoothly. Key challenges include the acceptance of the new screening strategy by patients and clinicians, as well as preventing a decrease in screening participation rates. In addition, the review identified the challenges associated with changes related to laboratory configuration, workflow, and human resourcing. There are several facilitators that can help with overcoming these barriers including education, stepwise rollout, organized screening programs, good IT systems, and HPV self-sampling.

The review emphasized that if a decision is made to adopt HPV testing for primary cervical cancer screening, implementation will need to be carefully planned and sufficient time and resources will need to be allotted to ensure structures and supports are in place – at the patient, clinician, laboratory, and systems level.

## References

1. HPV Testing for Primary Cervical Cancer Screening: A Health Technology Assessment [Internet]. Ottawa: CADTH; 2019. [cited 2019 Jun 16]. (CADTH optimal use report; vol.7; no.1b). Available from: <https://www.cadth.ca/sites/default/files/ou-tr/op0530-hpv-testing-for-pcc-report.pdf>

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