

Shifting from cytology to HPV testing for cervical cancer screening in Canada

Emily Delpero MD, Amanda Selk MD MSc

■ Cite as: *CMAJ* 2022 May 2;194:E613-5. doi: 10.1503/cmaj.211568

Infection with high-risk strains of the human papillomavirus (HPV) is a known prerequisite for developing cervical cancer.¹ Soon, a test for high-risk strains of HPV will replace the Papanicolaou (Pap) test for routine cervical cancer screening in Canada. Unlike the Pap test, which requires a cytopathologist to detect precancerous cervical cells, testing of a cervical sample for HPV subtypes uses polymerase chain reaction (PCR). Australia, the Netherlands and the United Kingdom have adopted the HPV testing model for cervical screening, and it is also endorsed by the American Cancer Society.² A recent review by the Canadian Agency for Drugs and Technologies in Health considered available evidence; its report concluded that HPV PCR testing of cervical samples is better at detecting precancer or cancer than Pap testing and would decrease the overall cost of screening.³ However, shifting to this new screening modality will mean overhauling existing algorithms for age and screening intervals, changing resource allocation and educating physicians and patients. We discuss why and how cervical screening will need to change in Canada with the adoption of the new test.

Current screening approaches acknowledge that Pap testing has a high specificity of 96.8%⁴ but a low sensitivity (55.4%), which means that screening misses almost half of existing abnormalities. A short interval for repeat testing (every 2–3 years, starting between the ages of 21 and 25, depending on the province) mitigates harm, as subsequent testing is likely to detect previously missed pathology in populations with relatively high disease prevalence.

Cervical cancer rates have declined in Canada in the 50 years since the introduction of cervical screening programs. Between 1978 and 2006, cervical cancer incidence dropped from 20.05 to 12.66 per 100 000,⁵ likely a result of population screening efforts (<https://s22457.pcdn.co/wp-content/uploads/2019/01/Cervical-Cancer-Screen-Quality-Indicators-Report-2016-EN.pdf>). In 2022, the projected age-standardized incidence rate for cervical cancer in Canada is 7.5 per 100 000.⁶ Primary prevention with routine vaccination against high-risk HPV for school-age children is expected to further decrease disease incidence. Recent data from the UK modelled reduced risk for precancerous lesions in vaccinated cohorts, with near elimination of these lesions in those who were immunized at middle-school age.⁷ A Swedish

Key points

- Testing for high-risk human papillomavirus (HPV) will soon replace the Pap test for primary cervical cancer screening in Canada, as it is a more sensitive test that has been shown to be cost-effective and safe.
- Given the success of school-based HPV vaccination programs, the prevalence of cervical cancer and its precursors is expected to decline, which is why a highly sensitive test is preferable to strengthen detection rates while minimizing false positives.
- Widespread public education is needed to overcome natural resistance to change and prevent misinterpretation of new recommendations as a merely cost-saving measure.

cohort study also linked HPV vaccination to reduced risk of cervical cancer at the population level.⁸ Rates of precancerous and cancerous cervical disease in Canada are expected to decline in a similar fashion. This will lower the positive predictive value of the Pap test.⁹ In the context of reducing disease prevalence and known limitations of Pap tests, a new strategy to maintain disease detection rates is needed.

Human papillomavirus DNA PCR testing has a higher sensitivity than cytology-based screening (94.6% v. 55.4%), but a lower specificity (94.1% v. 96.8%). This means that a greater proportion of patients without cervical disease are likely to receive a positive test result.¹⁰ However, with increasing HPV vaccine uptake and decreasing prevalence of high-risk HPV infection, HPV testing is expected to confer fewer false positives than Pap testing, while maintaining a strong negative predictive value.¹¹

According to current cervical screening pathways, patients with cytological abnormalities noted on Pap test are referred to colposcopy. Introducing HPV PCR testing for primary screening would alter existing parameters so that screening would start between the ages of 25 and 30 years. For patients who receive a negative result, testing would be repeated at 5-year intervals. Australia and the United States have implemented these parameters, with decisions based on balancing HPV test characteristics, the natural history of HPV infection and the harms of overscreening.

The benefit and safety of HPV primary screening in the Canadian context were shown in the 2018 publication of the landmark HPV For Cervical Cancer (FOCAL) trial.¹² The study randomized 19 009 women in British Columbia to primary screening with either HPV testing or routine cytology as per provincial guidelines. On conclusion of the trial, all participants underwent exit screening with both HPV and cytology testing; the risk ratio of finding a high-grade lesion was 0.42 in those randomized to upfront HPV test screening compared with routine care. This finding suggests that many lesions were missed by initial cytology testing and reinforces HPV testing as the better screening method.

Decisions to lengthen the cervical screening interval once the HPV PCR test is in routine use are based on the strong negative predictive value of HPV testing (> 99%).³ Researchers who conducted long-term follow-up of a cohort of people who participated in the FOCAL trial — the FOCAL DECADE cohort — found that the probability of finding a high-grade lesion 10 years after a single negative HPV test is less than 1%, with most lesions arising after 7 years or more.¹³ Screening more frequently could lead to harm (for example, psychological stress, additional medical visits or overtreatment of lesions that may regress without treatment) without improving detection.

The FOCAL trial also allowed for clear cost analysis, which can be hard to model. Although the cost of the HPV PCR test is greater than that of a cytology test, the cost is offset by less frequent testing, higher detection rates and fewer indeterminate results.¹⁴ Using trial data, researchers calculated that the mean cost per detected high-grade lesion was almost \$800 less in the HPV-screened arm than in the control arm (\$7551 v. \$8325).

Despite evident advantages of using HPV PCR as the primary test for cervical screening programs, developing and adopting a new screening system will require meticulous coordination of government funding, widespread changes to laboratory and data systems and multiple stakeholder buy-in (including the public, medical practitioners, the laboratory workforce and policy-makers). Without careful education for the public, raising the age of initial screening and reducing screening frequency could be viewed as governmental cost-cutting measures, with no benefit for patients.

The rollout of Australia's new screening program was hindered by widespread public and professional mistrust.¹⁵ The suggestion that the introduction of the new test was purely a cost-saving measure was propagated by the media and a nationwide petition with 70 000 signatures, initiated by a patient whose provider expressed apprehension about the change in policy. Australia's experience is instructive in highlighting the impact of addressing public perception.

Australia also noted a surge in colposcopy referrals with transition to primary HPV PCR screening because the test identifies more potential lesions up front. Referrals to colposcopy are projected to rise initially and then return to baseline and decrease as oncogenic HPV becomes less prevalent with vaccination. A 2018 review of trial evidence found that those younger than 35 years will be most affected by a change to HPV PCR screening, with a 2.3%–13.1% colposcopy referral rate versus 1.9%–4.7% in cytology screening.¹¹ Australia's experience, however, suggests a higher referral rate than these estimates. The country saw the

requirement for colposcopy more than double because of unanticipated contributing factors; e.g., providers screening earlier and more frequently than recommended, either owing to patient demand or provider judgment, possibly in part a result of lack of trust in the new paradigm.

In Canada, each province or territory will determine its own screening pathways based on population need. National guidance is expected to be released by mid to late 2022. To support health care providers and circumvent referrals to colposcopy driven by overscreening or uncertainty, clearly staged rollouts of new programs and ample lead-time to educate providers and address people's questions and concerns are needed. Engaging and educating providers will likely require sufficient forums for discussion and to answer questions, written materials (listserv communications, newsletters, pamphlets) addressing common concerns, and an accessible format or wiki for navigating new algorithms, similar to that available in the US (<https://www.asccp.org/mobile-app>).

A change to HPV PCR testing for cervical screening represents a rare instance in which a more sensitive screening test is found to be both more cost-effective and more responsive to the changing disease incidence that will result from successful HPV vaccination programs. However, international experience highlights the importance of early and broad public and provider education in ensuring a smooth and successful transition.

References

- Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999;189:12-9.
- Fontham ETH, Wolf AMD, Church TR, et al. Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. *CA Cancer J Clin* 2020;70:321-46.
- HPV testing for primary cervical cancer screening: recommendations report. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2019.
- Mayrand MH, Duarte-Franco E, Rodrigues I, et al. Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. *N Engl J Med* 2007;357:1579-88.
- Mosavi-Jarrahi A, Kliewer EV. Cervical cancer incidence trends in Canada: a 30-year population-based analysis. *J Obstet Gynaecol Can* 2013;35:620-6.
- Brenner DR, Poirier A, Woods RR, et al.; Canadian Cancer Statistics Advisory Committee. Projected estimates of cancer in Canada in 2022. *CMAJ* 2022;194:E601-7.
- Falcaro M, Castañón A, Ndlela B, et al. The effects of the national HPV vaccination programme in England, UK, on cervical cancer and grade 3 cervical intraepithelial neoplasia incidence: a register-based observational study. *Lancet* 2021;398:2084-92.
- Lei J, Ploner A, Elfström KM, et al. HPV vaccination and the risk of invasive cervical cancer. *N Engl J Med* 2020;383:1340-8.
- Franco EL, Mahmud SM, Tota J, et al. The expected impact of HPV vaccination on the accuracy of cervical cancer screening: the need for a paradigm change. *Arch Med Res* 2009;40:478-85.
- Melnikow J, Henderson JT, Burda BU, et al. Screening for cervical cancer with high-risk human papillomavirus testing: a systematic evidence review for the US Preventive Services Task Force. Rockville (MD): Agency for Healthcare Research and Quality; 2018.
- Grimes DR, Corry EMA, Malagón T, et al. Modeling cervical cancer screening strategies with varying levels of human papillomavirus vaccination. *JAMA Netw Open* 2021;4:e2115321.
- Ogilvie GS, van Niekerk D, Krajden M, et al. Effect of screening with primary cervical HPV testing vs cytology testing on high-grade cervical intraepithelial neoplasia at 48 months: the HPV FOCAL Randomized Clinical Trial. *JAMA* 2018;320:43-52.

13. Gottschlich A, van Niekerk D, Smith LW, et al. Assessing 10-year safety of a single negative HPV test for cervical cancer screening: evidence from FOCAL-DECADE Cohort. *Cancer Epidemiol Biomarkers Prev* 2021;30:22-9.
14. Cromwell I, Smith LW, van der Hoek K, et al. Cost-effectiveness analysis of primary human papillomavirus testing in cervical cancer screening: results from the HPV FOCAL Trial. *Cancer Med* 2021;10:2996-3003.
15. Smith M, Hammond I, Saville M. Lessons from the renewal of the National Cervical Screening Program in Australia. *Public Health Res Pract* 2019;29:2921914. doi: 10.17061/phrp2921914.

Competing interests: Amanda Selk is president of the Society of Canadian Colposcopists (SCC; no payment received) and co-author of upcoming national colposcopy guidelines from the SCC and Society of Gynecologic Oncology of Canada. Emily Delpero reports receiving an honorarium from Searchlight Pharma for a speaker introduction, outside the submitted work.

This article has been peer reviewed.

Affiliation: Department of Obstetrics and Gynecology, Mount Sinai Hospital; Department of Gynecology, Women's College Hospital, Toronto, Ont.

Contributors: Both authors contributed to the conception and design of the work, drafted the manuscript, revised it critically for important intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Content licence: This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY-NC-ND 4.0) licence, which permits use, distribution and reproduction in any medium, provided that the original publication is properly cited, the use is noncommercial (i.e., research or educational use), and no modifications or adaptations are made. See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>

Correspondence to: Emily Delpero, emily.delpero@mail.utoronto.ca