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2024 Updates to Cervical Cancer Screening in Canada

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Introduction

The landscape of cervical cancer screening in Canada is about to undergo a major shift from cytology-based screening to testing directly for the presence of high-risk strains of the human papilloma virus (HPV), the persistence of which is known to be a prerequisite for the development of almost all cases of cervical cancer. In 2018, the World Health Organization declared a call to action for the worldwide elimination of cervical cancer by 2040.[1] Subsequently the Canadian Partnership Against Cancer (CPAC) released an action plan outlining the necessary steps for Canada to reach this goal.[2] One of the 3 major priorities identified in the action plan is the transition to primary HPV testing.[2] This transition from screening to testing represents a major shift in infrastructure and also a shift in mindset for clinicians, policymakers, and the public. To help guide this transition, CPAC has collaborated with the Gynecologic Oncology Society of Canada (GOC) and the Society of Canadian Colposcopists (SCC) to release two open-access, evidence-based guidelines in June 2023. These guidelines address how to manage a positive HPV screening test,[3] and colposcopy in the context of primary HPV-screening.[4] This paper will outline the evolution of cervical cancer screening in Canada along with the rationale behind the transition to HPV testing. Also included is a discussion on the broad recommendations from the 2023 CPAC/GOC/SCC guidelines, as well as recommendations for age and interval of screening and special populations. Readers of this article in e-journal format can access the Canadian Guideline on the Management of a Positive Human Papillomavirus Test and Guidance for Specific Populations here. Readers may also access the 2023 Canadian Colposcopy Guideline: A Risk-Based Approach to Management and Surveillance of Cervical Dysplasia here.

Cervical Cancer Screening in Canada

Most Canadian provinces currently screen for cervical cancer using cytology-based screening, with many, but not all provinces having some type of organized screening program.[5] Screening for cervical cancer with cytology has been used in Canada since the 1940s, with the first organized screening programs in place starting in the 1960s.[6] Cytology-based testing, colloquially referred to as “Pap smears” or “Pap tests,” actually includes two distinct types of tests: the original Papanicolaou smear performed on a glass slide with fixative, and newer liquid-based cytology tests. In the 1980s it was discovered that HPV the causative agent for

cervical cancer; this finding led to the eventual development of HPV vaccines and the ability to test for viral DNA directly.[6] HPV testing is currently available as a follow up test for cytology to varying extents in some Canadian provinces.[5]

HPV DNA Testing

HPV nucleic acid testing has been known to outperform cytology for a number of years, and there have been major Canadian contributions to this research. For example, in 2007, the Canadian Cervical Cancer Screening Trial compared cytology-based testing and HPV DNA testing and showed HPV testing to be more sensitive for the detection of cervical high-grade squamous intraepithelial lesions (HSIL) or cancer (94.6% for HPV testing compared to 55.4% for Pap tests), with a similar specificity (94.1% for HPV testing, 96.8% for Pap tests).[7] Also in the Canadian context, the 2018 HPV FOCAL randomized clinical trial showed a reduced likelihood of HSIL cervical intraepithelial neoplasia grade 3 or worse (CIN3+) when primary HPV screening was used compared to the use of liquid-based cytology.[8] Several randomized controlled trials have provided evidence that HPV testing is also superior to cytology for reducing the incidence of and mortality from cervical cancer.[9] In recent years, a number of countries have implemented primary HPV screening, including the Netherlands and Australia in 2017, followed by the United Kingdom, the United States of America, and Finland.[10] Implementing primary HPV screening by these countries has allowed other countries to observe and learn from their experiences. Some Canadian provinces have already announced plans to transition to primary HPV testing.[2] In May 2023, Prince Edward Island became the first province in Canada to implement primary HPV screening for cervical cancer.[11] As of January 2024, British Columbia announced plans to imminently begin HPV-self swabbing for HPV with a phased plan for implementation of provide-collected primary HPV testing.[12]

The high sensitivity but lower specificity of the HPV test compared with that of the Pap test suggests that a triage test is recommended to improve the performance of the HPV test, and to reduce unnecessary referrals to colposcopy.[13] In Canada, the recommended triage tests are HPV genotyping for high-risk strains, followed by reflex liquid-based cytology.[3] In addition to these, other types of triage tests are actively under investigation.[3,10] As outlined in the 2023 CPAC/GOC/SCC guideline on management of a positive HPV test, if primary HPV testing produces a positive result, genotyping and/or reflex cytology should be performed to determine whether testing should be repeated at a predetermined interval versus direct referral to colposcopy. (**Table 1**)[3] There is currently no recommendation to modify screening based on vaccination history.[3]

Anticipated challenges in the implementation of primary HPV screening include the logistics of such a major shift in established programs, the need to educate clinicians and the public about why the change is recommended, and to manage the anticipated temporary doubling or tripling of colposcopy referrals that has occurred in other jurisdictions in which primary HPV-screening was implemented.[10] In the long-term, primary HPV testing reduces colposcopy referrals. (**Table 1.**)

Age and Interval of Screening with HPV Testing

The characteristics of HPV DNA tests compared to cytology-based tests allows the screening interval between HPV DNA tests to be extended to 5–10 years for the general population compared with the recommended interval of 3 years for cytology-based testing.[13] The 2023 CPAC/GCC/SCC guideline on HPV testing purposely avoids recommending an age at which screening is initiated.[3] This is because the decision should be determined provincially based on local population factors such as age of population, screening and vaccination uptake, as well as available resources.[9,10] HPV infection in young people is common and the virus is commonly cleared from the body. Screening for HPV at a very young age can lead to over-investigation and potentially unnecessary treatments.[10] Since 2013, the Canadian Task Force on Preventive Health Care has recommended initiating cytology-based screening at age 25.[14]; however, a number of provincial screening programs continue to initiate screening at age 21.[5] Other countries have recommended initiating screening at age 30 with intervals of 5–10 years, ending between age 65–74.[10] The World Health Organization recommends starting screening at age 30 for the general population with an interval of 5–10 years between HPV tests if negative.[13] Prince Edward Island chose to begin primary HPV-screening at age 25, with 5-year intervals, with routine

Indications for Referral to Colposcopy
• If positive for HPV 16 or 18, refer to colposcopy (reflex cytology should still be done)
• If positive for "other" high-risk HPV with ASCUS or LSIL reflex cytology, repeat HPV testing at 12 and 24 months and refer to colposcopy if persistently HPV positive at 24 months
• If positive for any genotype of high-risk HPV with high-grade reflex cytology (ASC-H, HSIL, AGC, AIS or suspicious for invasive cancer), refer directly to colposcopy
• If immunocompromised, refer to colposcopy with any genotype of high-risk HPV

Table 1. Indications for referral to colposcopy in the setting of primary HPV screening; *adapted from Zigras et al, 2023*.

Abbreviations: ASCUS: atypical squamous cells of undetermined significance, **LSIL:** low-grade squamous intraepithelial lesion, **ASC-H:** atypical squamous cells cannot rule out high-grade intraepithelial lesion, **HSIL:** high-grade squamous intraepithelial lesion, **AGC:** atypical glandular cells, **AIS:** adenocarcinoma in situ.

screening finishing at age 65.[11] The Canadian Task Force on Preventive Health Care is expected to make an updated national recommendation in 2025.[15] OncoSim has been developed by the Canadian Partnership Against Cancer to help provinces determine an appropriate age at which to initiate screening for their population. OncoSim is a free online cost-benefit analysis tool designed to help policy-makers estimate the effects of policy change on parameters such as life years and healthcare costs to help make decisions such as when to initiate screening.[2,16] It allows the comparison of cytology versus primary HPV-screening based on different eligibility criteria, participation rates, frequency of screening, and costs to help make public policy decisions such as age to initiate and to discontinue screening in a given population.[2]

Self-Screening Using HPV Testing

One unique possibility with primary HPV testing compared to cytology is the potential for samples to be self-collected. Sample collection can be performed at an office or at home, for example by mail-in programs or home visits.[10] The 2023 CPAC/GOC/SCC guideline on management of a positive HPV test recommends that self-sampling be offered as a method to increase uptake of testing in combination with face-to-face interactions, especially for under-screened populations, and potentially for the general population as well.[3] Self-sampling has been shown to increase participation in screening, be acceptable to participants, yield reliable results, and lead to reasonable attendance at colposcopy follow up.[3,17,18] To be able to perform reflex cytology as the guidelines recommend, if a vaginal self-sample tests positive for HPV, the next step is for a health care provider to collect a liquid-based cytology sample. Participants in the screening program should be aware that a pelvic exam may still be necessary based on the results of the test.

Special Populations

Immunocompromised Individuals: this population has an increased risk of cervical dysplasia and cervical cancer; however, for populations other than those living with human immunodeficiency virus (HIV), evidence is lacking.[19] The 2023 CPAC/GOC/SCC recommends that individuals with certain conditions, including HIV, inflammatory bowel disease or rheumatoid arthritis, if on immunosuppressants, systemic lupus erythematosus (regardless of whether they receive immunosuppressive therapies), and recipients of solid-organ transplants and hematopoietic stem cell transplants be referred directly to colposcopy if they have a positive test result for high-risk HPV, with similar management from colposcopy.[3] More evidence is required to

comment on whether modified screening pathways should otherwise be used.[3] For individuals living with HIV, the WHO suggests starting screening earlier and considering screening every 3–5 years with HPV DNA testing.[13]

After Hysterectomy: HPV vault testing is not recommended after hysterectomy for benign indications if there is no history of cervical dysplasia.[3] If there is a history of cervical dysplasia, HPV testing is used to determine if ongoing surveillance is indicated.[3] The 2023 CPAC/GOC/SCC guideline makes recommendations for the management of those with a low-grade squamous intraepithelial lesion (LSIL) or HSIL found on a hysterectomy specimen, including those with previously treated HSIL and negative or unknown HPV status prior to hysterectomy, hysterectomy performed for adenocarcinoma in situ (AIS), and those with a history of AIS who underwent a hysterectomy for other indications.[3] In most cases, if the HPV test result is negative, no further screening is indicated unless there is a history of AIS for which ongoing surveillance should continue.[3] This is a significant departure from previous cytology-based screening in which an extended duration of yearly Pap tests was recommended for these populations. The guidelines do not address screening after cervical carcinoma and suggest following recommendations consistent with gynecologic oncology.

Under-Screened Populations: CPAC's action plan for eliminating cervical cancer recognizes that under-screened groups must have increased participation in screening to eliminate cervical cancer.[2] Some provinces already have initiatives in place to increase the level of screening in these groups.[5] Offering HPV self-sampling within screening programs should be a consideration for all under-screened groups,[2,3] and has the potential to overcome a variety of barriers to participating in screening.[18]

- **Lesbian, Gay, Bisexual, Transgender, Queer/Questioning, Two Spirit Populations (LGBTQ2S+):** Transmen and women-who-have-sex-with-women are at risk for cervical cancer, though are more likely to have never been screened.[20] Any individual with a cervix who has ever been sexually active should be included in cervical cancer screening. Self-sampling should be offered if preferred by an individual, and providers should be respectful and create safe, inclusive environments for these people.[3]
- **First Nations, Inuit and Metis Populations:** These populations are under-screened. It is crucial to engage them in order to achieve Canada's goal of eliminating cervical cancer by 2040.[10] First Nations people have a higher incidence of cancers, including cervical cancer, and worse cancer-related outcomes.[21] Providers should increase their understanding of these communities, increase cultural safety and trauma-informed care, and offer cultural support and advocacy. Zigras et al. provide some specific suggestions on how providers can increase their understanding of this population.[3] This is another population in which self-screening may be of particular value, although engaging in colposcopy follow up after an abnormal HPV test result may be met with fear and mistrust, which underscores the importance of providers creating a safe environment.[3,21]
- **Those Living in Remote Areas, Immigrants, and Newcomers to Canada:** This is another example of under-served populations with barriers to access in which self-sampling has the potential to improve participation. Implementation of self-sampling access should be prioritized for these populations.[3,10]

Conclusion

The transition to primary HPV testing for cervical cancer secondary prevention is a major step toward reducing, and hopefully eliminating, cervical cancer. Improving HPV immunization rates and follow up of abnormal screening results is also crucial in eliminating cervical cancer.[2] Although some aspects of HPV testing may be faced with hesitation by clinicians and the public, especially the suggested later start for screening and longer screening intervals, HPV testing has a demonstrated capacity to reduce rates of cervical precancers and cancers, and considering the self-sampling option, is potentially less invasive, especially for vulnerable groups.

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