



Evidence-based Series 15-9 IN REVIEW

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Cervical Screening

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Original Report Date: May 20, 2005
Current Report Date: October 5, 2011

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The full Evidence-based Series (EBS) 15-9 is comprised of 3 sections and is available on the [CCO website](#) on the [PEBC Cancer Screening page](#)

- Section 1: Guideline Recommendations
- Section 2: Evidentiary Base
- Section 3: EBS Development Methods and External Review Process

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Journal Citations (Vancouver Style):

- Murphy J, Kennedy EB, Dunn S, McLachlin M, Fung Kee Fung M, Gzik D, et al. HPV testing in primary cervical screening: a systematic review and meta-analysis. *J Obstet Gynaecol Can.* 2012;34(5):443-52.
- Murphy J, Kennedy EB, Dunn S, McLachlin M, Fung Kee Fung M, Gzik D, et al. Cervical screening: a guideline for clinical practice in Ontario. *J Obstet Gynaecol Can.* 2012;34(5):453-58.

Citation (Vancouver Style): Murphy J, Kennedy E, Dunn S, Fung Kee Fung M, Gzik D, McLachlin CM, et al. Cervical Screening. Toronto (ON): Cancer Care Ontario; 2011 Oct 5 [In Review 2016 Apr]. Program in

In Review



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Evidence-based Series 15-9: Section 1

Cervical Screening: Guideline Recommendations

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QUESTIONS

In Ontario, in the context of an organized cervical screening program:

1. What is the optimal primary cervical screening method (i.e., human papillomavirus [HPV] DNA testing and/or cytology testing)?

In average risk, asymptomatic women:

2. What is the most appropriate age for the initiation of cervical screening?
3. What is the optimal interval between cervical screenings?
4. What is the most appropriate age for the cessation of cervical screening?

TARGET POPULATION

Average risk asymptomatic women in Ontario, Canada.

INTENDED USERS

This guideline is intended for family physicians, other primary care providers, and gynecology specialists involved in screening women for cervical cancer and its precursors.

INTRODUCTION

The Ontario Cervical Screening Program (OCSP) is currently being relaunched to incorporate an organized call and recall component. This relaunch has necessitated a review of evidence related to the research questions listed above and an update of the relevant portions of the Program in Evidence-based Care (PEBC) May 2005 guideline *Cervical Screening* (1). The updated guideline will help the OCSP to realize its long-term goals of reducing the incidence of and mortality from cervical cancer through an organized screening program and improving the capacity of providers to engage in organized cervical screening. It will also

address the 2011-2014 Ontario Cancer Plan (2) goal of creating evidence-based guidelines for cervical cancer screening.

Evidence clearly indicates that there is a role for HPV testing in primary screening, and, thus, the primary recommendations presented in Part 1 of this guideline are for HPV-based testing for women 30 years of age and over. The proposed algorithm (Figure 1) assumes the existence of an organized province-wide screening program.

There is lesser quality evidence at this time for the appropriate screening algorithm for women under 30. For this reason, and because HPV testing is not currently funded in the province and the components of an organized screening program are in the process of being put in place, a set of interim recommendations (Section 1, Part 2) are also provided that include the younger age group and acknowledge the current standard of cytology-based testing. The goal of the interim recommendations is to provide a bridge to the time when HPV testing for primary screening is funded in Ontario. Because screening for cervical cancer is a quickly evolving field, the HPV testing-based algorithm, the optimal age for screening initiation, and a method of screening for women younger than 30 years should be reviewed prior to implementation. A comparison of recommendations contained in this guideline and in the previous version published in 2005 is presented in Table 1. A table of screening test results terminology and a glossary of terms are provided in Appendices 1 and 2, respectively. For more information on HPV and the development of cervical cancer, details of the systematic review, and discussion of the impact of adoption of HPV testing for primary screening, please see Section 2 of this report.

Table 1. Summary of PEBC screening recommendations for Ontario: 2005-2013.

Year (Section)	Evidence base	Implementation timeframe	Primary screening test	Age of screening initiation	Screening interval	Age of screening cessation*
2011 (Part 1)	Evidence- and consensus-based (up to 2011)	2013 (anticipated implementation of HPV testing in the Province of Ontario)	Women 30+: HPV testing; women <30: to be determined	To be determined at the time that HPV is implemented	Every 5 years with a negative HPV test result	65
2011 (Interim) (Part 2)	Evidence and Consensus-based	2011-2012	Cytology testing	21 years of age	Every three years	70
2005 (1)	Evidence-based (up to 2005)	2005-2010	Cytology testing	Within 3 years of initiation of sexual activity	Annually until three negative tests, then every 2-3 years	70

Abbreviation: HPV = human papillomavirus. *Provided that an adequate negative screening history has been established.

PART 1: RECOMMENDATIONS FOR CERVICAL SCREENING WITH HPV DNA TESTING

RECOMMENDATION

Primary Screening Test

HPV DNA testing of cells collected from the cervix is recommended for primary cervical screening. Cytology screening, which was recommended for primary screening in the previous version of this guideline, is now recommended only in the event of a positive HPV DNA test result (see HPV screening algorithm, Figure 1). Interim recommendations are provided in Section 1, Part 2 (Interim Recommendations), because HPV testing is not funded at this time for primary screening in Ontario.

KEY EVIDENCE

HPV testing

Seven randomized controlled trials (RCTs) (3-8) have been conducted to assess the performance of HPV testing in primary screening. The trials assessed the rates of cervical intraepithelial neoplasia grade 2 or grade 3 (CIN2 or CIN3), either at a baseline screening round or over two screening rounds. CIN2 is a useful indicator because it is often the threshold for clinical management. CIN3 is less likely than lower grades of CIN to regress or resolve without treatment and so is a useful predictor of the risk for cervical cancer. The results showed that:

- HPV testing consistently detected significantly more CIN2 and CIN3 in the baseline screening round than did cytology-based testing. HPV testing detected fewer CIN2 or more severe (CIN2+) cases in the subsequent screening round, indicating a lead time gain with HPV testing.
- The one trial that had sufficient sample size to report incidence and mortality due to cervical cancer found a significant reduction with HPV testing but not with cytology testing, compared to standard care (9).
- There was no significant difference in the number of invasive cancers detected in the baseline screening round in the New Technologies in Cervical Cancer trial (8) comparing HPV testing and cytology testing. In the subsequent screening round, no cases of cancer were found in the HPV-testing group, while nine cases were found in the cytology-testing group. A high number of the cancers detected in the second round in the cytology group were adenocarcinomas (10). This is consistent with previous reports that cytology is less effective in preventing adenocarcinomas than squamous cell carcinomas (approximately 20% of cervical cancers in Ontario are adenocarcinomas) (11).

Cytology Triage of HPV Positive Results

- Due to the higher sensitivity of HPV testing compared to conventional cytology, the rate of colposcopy referral with HPV testing alone is higher than the rate with conventional cytology. For example, in the Canadian Cervical Cancer Screening Trial (CCCaST) RCT, the rate of referral to colposcopy after a positive HPV test alone was 6.1%, compared to a referral rate of 2.6% for conventional cytology results of atypical squamous cells of undetermined significance (ASCUS) (3).
- A triage test can reduce the number of colposcopy referrals and increase the specificity of the screening algorithm. In CCCaST, HPV with Pap triage resulted in a 1.1% rate of referral based on ASCUS (3). The Finnish Public Health Trial found the frequency of colposcopy referrals was 1.2% in both the conventional cytology arm at a threshold of low-grade squamous intraepithelial lesions (LSIL) and the HPV with cytology triage arm of their trial

(12).

QUALIFYING STATEMENT

- The recommendation for HPV testing is applicable only in the context of an organized screening program with an adequate database infrastructure that allows for an invitation to screening at recommended intervals, and a follow-up of women with abnormal test results.
- HPV testing has been shown to be more effective for women 30 years of age and older (see Age of Screening Initiation below).
- Women who have never been sexually active¹ do not require cervical screening.

RECOMMENDATION

Age of Screening Initiation

It is the opinion of the Cervical Screening Guideline Working Group (the Working Group) that there is insufficient evidence at this time to make a recommendation for the age at which to begin cervical screening using HPV testing as the primary screen. HPV testing performs better for women 30 and over compared to younger women because the rate of transient infections is higher in the younger age group; therefore, the screening algorithm in the following recommendation is presented for women 30-65 years of age.

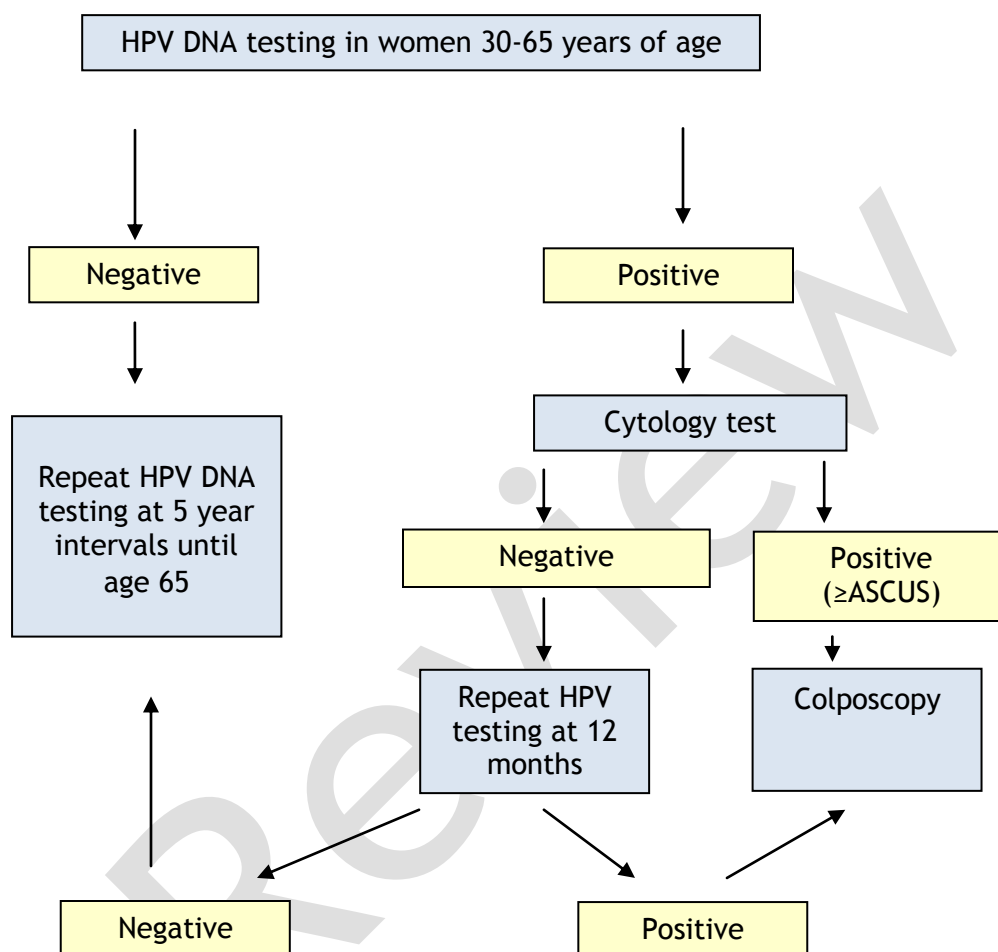
RECOMMENDATION

Screening Interval (Women 30-65)

Screening interval recommendations are according to the algorithm presented in Figure 1. For women aged 30-65, HPV DNA testing is to occur at five-year intervals after an initial negative result, which is a change from the recommendation for repeat cytology testing every two to three years contained in the 2005 version of this guideline. HPV-positive tests should be assessed with cytology testing and not referred directly to colposcopy. Repeat HPV testing for results of HPV positive/cytology negative should be conducted after one year.

¹ Sexually active is defined as vaginal intercourse and vaginal/oral and/or vaginal/digital sexual activity.

Figure 1: Primary cervical screening with HPV testing (women 30-65)² (adapted from Cuzick et al. 2008 (13)).



KEY EVIDENCE

The proposed HPV testing algorithm is based on a combination of evidence from cohort studies, the natural history of HPV infections, and the consensus of the Working Group.

Five-Year Interval after HPV Negative Results

- Six years after a negative HPV test, pooled cohort data found a cumulative incidence rate for CIN3+ of 0.27% (95% CI, 0.12 to 0.45), which was lower than the rate after three years with a negative cytology test (0.51%; 95% CI, 0.23 to 0.77) (14). This indicates that retesting at five-year intervals would entail a low level of risk.
- The risk of CIN3+ after a negative HPV test is low: in a Danish cohort study the 12-year absolute risk of CIN3+ after a negative HPV DNA test in women with normal cytology was 3.0% (95% CI, 2.5 to 3.5%) (15).

² This screening algorithm should be reviewed for currency prior to its implementation as results from subsequent screening rounds of the HPV RCTs are expected in the next one to two years.

One-Year Interval with HPV Positive/Cytology Negative Results

The short-term persistence of HPV infection for at least one year is an important predictor of CIN2+ (16). In women who tested HPV positive at enrolment and negative after about one year (nine-21 months), the cumulative incidence of CIN2+ after three years was 1.2% (95% CI, -0.2 to 2.5). The three-year cumulative incidence of CIN2+ in women who tested positive for carcinogenic HPV at study enrolment and again after approximately one year was 17.0% (95% CI, 12.1 to 22.0) (16). Consequently, referral to colposcopy after two consecutive positive HPV tests occurring a year apart is recommended, even in the event of initially negative cytology results.

QUALIFYING STATEMENTS

The screening algorithm (Figure 1) should be reviewed for currency prior to implementation.

A variation on this algorithm includes genotyping for HPV 16 and/or HPV 18 immediately after a positive HPV test and cytology results of normal, ASCUS or LSIL, based on the rationale that HPV 16 has been shown to be more persistent and more often associated with high-grade lesions, and HPV 18 is more often associated with difficult to detect lesions in the endocervical canal (13). Positivity for either of these types may require immediate colposcopy.

RECOMMENDATION**Age of Screening Cessation**

Screening may be discontinued after the age of 65 provided there is an adequate negative screening history in the previous 10 years (i.e., two or more negative tests) and a final negative HPV test at age 65. Women who do not meet these requirements should continue with screening at recommended intervals. This is a change from the previous recommendation of cessation at age 70 (1).

KEY EVIDENCE

This recommendation is the consensus of the authors, taking into account the low rate of cervical cancer in this age group among women who have previously been adequately screened, the potential discomfort of the procedure, and difficulties with visualization of the squamocolumnar junction in older women.

PART 2: INTERIM RECOMMENDATIONS (TO BE FOLLOWED UNTIL HPV TESTING IS FUNDED)

INTERIM RECOMMENDATION

Primary Screening Test

On an interim basis, the authors endorse the recommendation contained in the 2005 version of this guideline: primary screening with cytology testing (1).

KEY EVIDENCE

This recommendation is the opinion of the authors based on the systematic review conducted for the previous version of this guideline (1).

QUALIFYING STATEMENTS

- Women with Pap tests that lack transformation zone components (i.e., endocervical and/or metaplastic cells) may continue screening at the regular intervals recommended by the guideline. Repeated samples lacking transformation zone may require further investigation.
- The above statement does not include women with test results of “unsatisfactory”, who should undergo repeat screening in three months. This qualifying statement is the opinion of the Working Group based on the clinical experience that a shorter waiting period may result in the detection of reactive changes as a result of the first screening test.
- The Working Group maintains the recommendations for screening of special populations contained in the 2005 guideline:
 - Immunocompromised women (e.g., those currently taking long-term immunosuppressants, those who are HIV positive) should receive annual screening.
 - Screening can be discontinued in women who have undergone a total hysterectomy for benign causes with no history of cervical dysplasia or HPV. Women who have undergone subtotal hysterectomy (with an intact cervix) should continue screening according to the guidelines.
 - Indications for screening frequency for pregnant women should be the same as for women who are not pregnant. Manufacturers’ recommendations for the use of individual screening tools in pregnancy should be considered.
 - Women who have sex with women should follow the same cervical screening regimen as women who have sex with men.

INTERIM RECOMMENDATION

Age of Screening Initiation

Cytology testing should commence at 21 years of age for sexually active women.

KEY EVIDENCE

Lower quality evidence was available for the questions regarding the age of initiation of cervical screening. Three case-control studies were found that addressed the questions of initiation (17-19). The results of these studies were mixed, with a trend towards higher efficacy of screening for older women. There were no studies found that directly assessed the optimal age of initiation of cervical screening with HPV testing as the primary screen.

RATIONALE

- After weighing the available evidence, the authors of this guideline have concluded that the harms of screening women under 21 years of age significantly outweigh the benefits. In the opinion of the authors, the potential for adverse reproductive outcomes with treatment, anxiety related to the testing procedure, and the anxiety and potential stigma

associated with positive test results considerably outweigh the benefits of screening in women younger than 21 years of age (20-23), given the relatively high rate of HPV infection (24), rarity of cervical cancer in women under 25 years, and the up to decades-long time period of progression from HPV infection to cervical cancer (25).

- In the opinion of the Working Group, evidence regarding the necessity, utility, and/or effectiveness of screening in women 21 to 24 years is not as clear; the authors of this guideline are not convinced that the harms outweigh the benefits of screening for these women. Therefore, the consensus is that lesions in these women should be detected and treated where appropriate in order to minimize the potential for their progression to cervical cancer.
- The guideline authors do recognize that there is also a potential for harm with screening. The potential harms related to treatment of CIN are adverse reproductive outcomes, including premature rupture of membranes, low birth weight, and preterm delivery (22). The early detection and treatment of CIN3 in young women, however, might prevent some cancers developing to a stage where treatment could result in compromised fertility. Based on the information available at this time, the authors of this guideline consider that the benefit of eliminating potential cases of invasive cervical cancer in women 21-24 years of age outweighs the reproduction-related harms, as well as the potential anxiety, fear, and uncertainty related to abnormal screening tests, intensified screening, colposcopy, biopsy, and treatment for CIN.

QUALIFYING STATEMENTS

- Women who are not sexually active³ by age 21 may delay cervical screening.
- Women who have never been sexually active do not require cervical screening.
- The interim recommendation to begin screening at 21 years of age should be reviewed within 24 months of the publication of this guideline.
- As HPV-vaccinated women reach the age of screening initiation, there may be impact on the screening recommendations.

KEY EVIDENCE

The key evidence for this recommendation is presented in Section 2 (systematic review section) of the 2005 PEBC guideline *Cervical Screening* (1).

INTERIM RECOMMENDATION

Screening Interval

Women should be screened every three years.

KEY EVIDENCE

The previous guideline recommended three annual negative screens before lengthening the screening interval to two to three years. Evidence presented in the previous version of this guideline showed that the excess risk with screening every three years compared to annually was approximately three additional cases of cervical cancer per 100,000 women (26).

A modelling study conducted in Australia found that increasing the recommended screening interval from two years to three years with cytology-based testing would result in no substantial change to incidence and mortality due to cervical cancer (27).

³ Sexually active is defined as vaginal intercourse and vaginal/oral and/or vaginal/digital sexual activity.

INTERIM RECOMMENDATION

Age of Screening Cessation

The authors endorse the age of cessation of cytology-based testing presented in the 2005 version of this guideline:

- Screening may be discontinued after the age of 70 if there is an adequate negative cytology screening history in the previous 10 years (i.e., three to four negative cytology tests).

KEY EVIDENCE

Key evidence for this recommendation is presented in Section 2 (systematic review section) of the 2005 PEBC guideline *Cervical Screening* (1).

Recommended Management for Women with Abnormal Cytology

Management recommendations were not included in the scope of the current guideline. The algorithm for the management of abnormal results from the previous version of this guideline has been appended, however, as its recommendations still apply to the interim cytology-based guidelines provided here. Please see Appendix 3 (Section 1, page 19). If the evidence base for these recommendations is required, please email ccopgi@mcmaster.ca.

FUTURE RESEARCH

Results from further screening rounds of several of the RCTs included in the evidence base for this guideline are anticipated (Table 2). These results should further inform the optimal screening algorithm for women 30 years of age and older and the optimal age for commencing cervical screening. An international agreement has been reached to conduct future meta-analyses of the HPV screening trials and to synthesize evidence on new methods for cervical cancer prevention (28).

Table 2. Anticipated results from randomized trials.

Study acronym (ID number)	Study initiation date	Study end date	Further results anticipated?
CCCaST (ISRCTN57612064)	September 2002	July 2007	Yes; long-term efficacy data (personal communication, Eduardo Franco, January 2011).
NTCC (ISRCTN81678807)	February 2002	December 2004	Yes; A cost-benefit analysis is underway (10). Also, the group is updating the follow-up of a third screening round (personal communication, Guglielmo Ronco, May 2011).
ARTISTIC (ISRCTN25417821)	June 2001	November 2009	Yes; the ARTISTIC trial is continuing to follow women while maintaining the randomised concealment of HPV testing results for a further three-year round of screening (29).
FPHT (ISRCTN 23885553)	January 1999	December 2020	Yes; the group intends to rescreen women according to the same allocation at least twice; publications based on this ongoing follow-up are anticipated (30).
POBASCAM (ISRCTN20781131)	January 1999	September 2007	No
Sankaranarayanan	October 1999	2007	No
Swedescreen (NCT00479375)	May 1997	May 2007	No

Abbreviations: ARTISTIC = A Randomized Controlled Trial of Human Papillomavirus Testing in Primary Cervical Screening (UK = United Kingdom), CCCaST = Canadian Cervical Cancer Screening Trial, FPHT = Finnish Public Health Trial, NTCC = New Technologies in Cervical Cancer (Italy), POBASCAM = Population Based Screening Study Amsterdam (the Netherlands).

The HPV FOCAL study (Trial Registration No. ISRCTN79347302) is being conducted by the BC (British Columbia) Cancer Agency, in collaboration with the BC Centre for Disease Control, the University of British Columbia, McGill University, and healthcare providers in Metro Vancouver and Greater Victoria. In a Canadian context, this study aims to establish the efficacy of human HPV testing as a stand-alone screening test with cytology triage of HPV positive women, establish an appropriate screening interval for HPV negative women, and determine cost-effectiveness of HPV testing as a primary screening test.

Other HPV testing strategies under study are based on molecular markers and include viral load, genotyping, testing for the RNA of the viral oncogenes E6 and E7, and testing for the overexpression of the p16-INK4A protein (31).

As research continues into the risk factors for cervical cancers and the different type-specific and other tests evolve, screening algorithms will become increasingly more complex. In response to this, a group is developing a tool to predict the risk for a woman of having or developing cervical precancer. These risk estimates could be used to make referral and screening interval decisions (32) and may be considered for implementation in future update of this guideline.

RELATED GUIDELINES

- Fung-Kee-Fung M, Howlett R, Oliver T, Murphy J, Elit L, Strychowsky J, et al. The optimum organization for the delivery of colposcopy service in Ontario. *J Low Genit Tract Dis.* 2010 Jan;14 (1):1-21. doi: 10.1097/LGT.0b013e3181a911b8.
- Stewart DE, Johnston M, Gagliardi A, Howlett R, Barata P, Lewis N, et al. Self-collected samples for testing of oncogenic human papillomavirus. *J Obstet Gynaecol Can.* 2007 Oct;29(10):817-28.

Funding

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

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REFERENCES

1. McLachlin CM MV, Murphy J, Fung Kee Fung M, Chambers A; Cervical Screening Guidelines Development Committee of the Ontario Cervical Screening Program, Gynecology Cancer Disease Site Group of Cancer Care Ontario. Cervical screening: a clinical practice guideline. Program in Evidence-based Care Special Report Evidence-based Series. Toronto (ON): Cancer Care Ontario; 2005 May.
2. Cancer Care Ontario. Ontario Cancer Plan 2011-2015. Toronto (ON): Cancer Care Ontario; 2011.
3. Mayrand M, Duarte-Franco E, Rodrigues I, Walter SD, Hanley J, Ferenczy A, et al. Human papillomavirus DNA versus papanicolaou screening tests for cervical cancer. *New Engl J Med*. 2007;357(16):1579-88.
4. Naucler P, Ryd W, Tornberg S, Strand A, Wadell G, Elfgren K, et al. Human papillomavirus and Papanicolaou tests to screen for cervical cancer. *N Engl J Med*. 2007;357(16):1589-97.
5. Sankaranarayanan R, Nene BM, Shastri SS, Jayant K, Muwonge R, Budukh AM, et al. HPV screening for cervical cancer in rural India. *N Engl J Med*. 2009;360(14):1385-94.
6. Bulkman NW, Berkhof J, Rozendaal L, van Kemenade FJ, Boeke AJ, Bulk S, et al. Human papillomavirus DNA testing for the detection of cervical intraepithelial neoplasia grade 3 and cancer: 5-year follow-up of a randomised controlled implementation trial. *Lancet*. 2007;370(9601):1764-72.
7. Arbyn M, Anttila A, Jordan J, Ronco G, Schenck U, Segnan N, et al. European guidelines for quality assurance in cervical cancer screening. Second edition - summary document. *Ann Oncol*. 2010;21(3):448-58.
8. Kitchener HC, Almonte M, Thomson C, Wheeler P, Sargent A, Stoykova B, et al. HPV testing in combination with liquid-based cytology in primary cervical screening (ARTISTIC): a randomised controlled trial. *Lancet Oncol*. 2009;10(7):672-82.
9. Sankaranarayanan R, Nene BM, Shastri SS, Jayant K, Muwonge R, Budukh AM, et al. HPV screening for cervical cancer in rural India. *N Engl J Med*. 2009;360(14):1385-94.
10. Ronco G, Giorgi-Rossi P, Carozzi F, Confortini M, Dalla Palma P, Del Mistro A, et al. Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. *Lancet Oncol*. 2010;11(3):249-57.
11. Cancer Care Ontario and Canadian Cancer Society (Ontario Division). Insight on cancer. Toronto (ON): Cancer Care Ontario; Canadian Cancer Society (Ontario Division); 2005 Oct.
12. Leinonen M, Nieminen P, Kotaniemi-Talonen L, Malila N, Tarkkanen J, Laurila P, et al. Age-specific evaluation of primary human papillomavirus screening vs conventional cytology in a randomized setting. *J Natl Cancer Inst*. 2009;101(23):1612-23.
13. Cuzick J, Arbyn M, Sankaranarayanan R, Tsu V, Ronco G, Mayrand MH, et al. Overview of human papillomavirus-based and other novel options for cervical cancer screening in developed and developing countries. *Vaccine*. 2008;26 Suppl 10:K29-41.
14. Dillner J, Rebolj M, Birembaut P, Petry KU, Szarewski A, Munk C, et al. Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening: joint European cohort study. *BMJ*. 2008;337:a1754.
15. Kjaer SK, Frederiksen K, Munk C, Iftner T. Long-term absolute risk of cervical intraepithelial neoplasia grade 3 or worse following human papillomavirus infection: role of persistence. *J Natl Cancer Inst*. 2010;102(19):1478-88.
16. Castle PE, Rodriguez AC, Burk RD, Herrero R, Wacholder S, Alfaro M, et al. Short term persistence of human papillomavirus and risk of cervical precancer and cancer: population based cohort study. *BMJ*. 2009;339:b2569.
17. Sasieni P, Castanon A, Cuzick J. Effectiveness of cervical screening with age: population

- based case-control study of prospectively recorded data. *BMJ*. 2009;339.
18. Andrae B, Kemetli L, Sparen P, Silfverdal L, Strander B, Ryd W, et al. Screening-preventable cervical cancer risks: evidence from a nationwide audit in Sweden. *J Natl Cancer Inst*. 2008;100(9):622-9.
 19. Crocetti E, Battisti L, Betta A, Palma PD, Paci E, Piffer S, et al. The cytological screening turned out effective also for adenocarcinoma: a population-based case-control study in Trento, Italy. *Eur J Cancer Prev*. 2007;16(6):564-7.
 20. Rogstad KE. The psychological impact of abnormal cytology and colposcopy. *Br J Obstet Gynaecol*. 2002;109(4):364-8.
 21. Prendiville W. The treatment of CIN: what are the risks? *Cytopathology*. 2009;20(3):145-53.
 22. Kyrgiou M, Koliopoulos G, Martin-Hirsch P, Arbyn M, Prendiville W, Paraskeva E. Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. *Lancet*. 2006;367(9509):489-98.
 23. Arbyn M, Kyrgiou M, Simoons-Smit AM, Raifu AO, Koliopoulos G, Martin-Hirsch P, et al. Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: meta-analysis. *BMJ*. 2008;337:a1284.
 24. Sellors JW, Mahony JB, Kaczorowski J, Lytwyn A, Bangura H, Chong S, et al. Prevalence and predictors of human papillomavirus infection in women in Ontario, Canada. Survey of HPV in Ontario Women (SHOW) Group. *CMAJ*. 2000;163(5):503-8.
 25. Schiffman M, Wentzensen N, Wacholder S, Kinney W, Gage JC, Castle PE. Human Papillomavirus Testing in the Prevention of Cervical Cancer. *J Natl Cancer Inst*. 2011;103:1-16.
 26. Sawaya GF, McConnell KJ, Kulasingam SL, Lawson HW, Kerlikowske K, Melnikow J, et al. Risk of cervical cancer associated with extending the interval between cervical-cancer screenings. *N Engl J Med*. 2003;349(16):1501-9.
 27. Creighton P, Lew J-B, Clements M, Smith M, Howard K, Dyer S, et al. Cervical cancer screening in Australia: modelled evaluation of the impact of changing the recommended interval from two to three years. *BMC Public Health*. 2010;10:734.
 28. Arbyn M, Cuzick J. International agreement to join forces in synthesizing evidence on new methods for cervical cancer prevention. *Cancer Lett*. 2009;278(1):1-2.
 29. UK NHS Cervical Screening Programme. ARTISTIC trial [Internet]. 2011. [cited 2011 Oct 07]. Available from: <http://www.cancerscreening.nhs.uk/cervical/artistic-trial.html>.
 30. Anttila A, Kotaniemi-Talonen L, Leinonen M, Hakama M, Laurila P, Tarkkanen J, et al. Rate of cervical cancer, severe intraepithelial neoplasia, and adenocarcinoma in situ in primary HPV DNA screening with cytology triage: randomised study within organised screening programme. *BMJ*. 2010;340.
 31. Ronco G, Giorgi Rossi P. New paradigms in cervical cancer prevention: opportunities and risks. *BMC Womens Health*. 2008;8:23.
 32. Katki HA, Wacholder S, Solomon D, Castle PE, Schiffman M. Risk estimation for the next generation of prevention programmes for cervical cancer. *Lancet Oncol*. 2009;10(11):1022-3.
 33. National Library of Medicine. MedlinePlus medical dictionary [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2011 Jul 11 [cited 2011 Oct 07]. Available from: <http://www.nlm.nih.gov/medlineplus/mplusdictionary.html>.
 34. The AGREE Collaboration. Writing Group: Cluzeau FA, Burgers JS, Brouwers M, Grol R, Mäkelä M, Littlejohns P, et al. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. *Qual Safe Health Care*. 2003;12(1):18-23.
 35. British Medical Journal Evidence Centre. Clinical evidence glossary [Internet]. London:

BMJ Publishing Group; 2011 [cited 2011 Oct 07]. Available from: <http://clinicalevidence.bmj.com/ceweb/resources/glossary.jsp>.

36. Parboosingh EJ, Anderson G, Clarke EA, Inhaber S, Kaegi E, Mills C, et al. Cervical cancer screening: are the 1989 recommendations still valid? National Workshop on Screening for Cancer of the Cervix. CMAJ. 1996;154(12):1847-53.

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Appendix 1. Screening test results terminology.

Cytology Diagnosis	Histology Diagnosis	Other terms
Atypical squamous cells (ASC):		
Atypical squamous cells of uncertain significance (ASCUS)		Borderline changes
Atypical squamous cells: cannot exclude high grade squamous (ASC-H)		
Low-grade squamous intraepithelial lesion (LSIL)	Cervical intraepithelial neoplasia grade 1 (CIN1)	Mild dysplasia
High-grade squamous intraepithelial lesion (HSIL)	CIN2	Moderate dysplasia
	CIN3, carcinoma in situ	Severe dysplasia
Squamous cell carcinoma (SCC)		
Atypical glandular cells - not otherwise specified (AGC-NOS)		
Atypical glandular cells (AGC-neoplastic)		
Adenocarcinoma in situ (AIS)		

Appendix 2. Glossary of terms.

Adenocarcinoma - a malignant tumour originating in glandular epithelium (33).

AGREE II - the Appraisal of Guidelines for Research and Evaluation, an international tool to assess the quality and reporting of practice guidelines (34).

Case-control study - a study design that examines a group of people who have experienced an event (usually an adverse event) and a group of people who have not experienced the same event, and looks at how exposure to suspect (usually noxious) agents differed between the two groups. This type of study design is most useful for trying to ascertain the cause of rare events, such as rare cancers (35).

Cervical dysplasia - the abnormal microscopic appearance of cells on the surface of the cervix. Although it is not cancer, dysplasia is considered a precancerous condition (33).

Cervical intraepithelial neoplasia - dysplasia that is seen on a cervical biopsy is called cervical intraepithelial neoplasia (CIN) and is grouped into three categories:

- CIN I -- mild dysplasia
- CIN II -- moderate to marked dysplasia
- CIN III -- severe dysplasia to carcinoma in situ (33)
-

Cohort study - a non-experimental study design that follows a group of people (a cohort) and then looks at how events differ among people within that group. A study that examines a cohort, which differs in respect to exposure to some suspected risk factor (e.g., smoking), is useful for ascertaining whether exposure is likely to cause specified events (e.g., lung cancer). Prospective cohort studies (which track participants forward in time) are more reliable than retrospective cohort studies (35).

Colposcopy - a magnifying instrument designed to facilitate visual inspection of the vagina and cervix (33).

Conventional cytology - see Pap smear.

Cotesting - for the purposes of this guideline, cotesting refers to cervical screening using the combination of cytology plus HPV testing concurrently.

Cytology - a branch of biology dealing with the structure, function, multiplication, pathology, and life history of cells (33).

Dysplasia - abnormal growth or development (as of organs or cells) (33).

Epithelium - a membranous cellular tissue that covers a free surface or lines a tube or cavity of an animal body and that serves especially to enclose and protect the other parts of the body, to produce secretions and excretions, and to function in assimilation (33).

Genotype - all or part of the genetic constitution of an individual or group (33).

Hazard ratio (HR) - broadly equivalent to relative risk (RR); useful when the risk is not

constant with respect to time. The HR uses information collected at different times and is typically used in the context of survival over time. If the HR is 0.5 then the RR of dying in one group is half the risk of dying in the other group (35).

Histology - a branch of anatomy that deals with the minute structure of animal and plant tissues as discernible with the microscope (33).

Human papillomavirus (HPV) - a double-stranded DNA virus of the genus *Papillomavirus* (species *Human papillomavirus*) that has numerous genotypes causing various human warts (e.g., common warts of the extremities, plantar warts, genital warts), including some associated with the production of cervical cancer (33).

Intraepithelial - occurring in or situated among the cells of the epithelium (33).

Invasive cervical cancer - cancer cells tending to spread, especially tending to invade healthy tissue (33).

Lesion - an abnormal change in the structure of an organ or a body part due to injury or disease, especially a change that is circumscribed and well defined (33).

Natural history - natural development of something (e.g., organism, disease) over a period of time (33).

Negative predictive value (NPV) - the chance of not having a disease given a negative test result (not to be confused with *specificity*, which is the other way round) (35).

Oncogene - gene having the potential to cause a normal cell to become cancerous, e.g. viral oncogenes E6 and E7 (33).

Opportunistic screening program - a screening program that lacks the features of an organized screening program (see below).

Organized screening program - a screening program that is characterized by information systems linked to population databases to facilitate the recruitment of target populations, invitation and recall at appropriate intervals, communication of abnormal results, and follow-up and monitoring of program quality (36).

Pap smear - a method, or a test based on it, for the early detection of cancer, especially of the uterine cervix, that involves staining exfoliated cells by a special technique that differentiates between diseased and healthy tissue—also called a Papanicolaou smear, Papanicolaou test, or Pap test (33) and referred to in this guideline as ‘conventional cytology’.

Positive predictive value (PPV) - the chance of having a disease given a positive test result (not to be confused with *sensitivity*, which is the other way round) (35).

Precancerous lesions - lesions that are tending to become cancerous (33).

Randomized controlled trials (RCTs) - a trial in which participants are randomly assigned to two or more groups: at least one (the experimental group) receiving an intervention that is

being tested and the other (the comparison or control group) receiving an alternative treatment or placebo. This design allows an assessment of the relative effects of interventions (35).

Relative detection rate - the ratio of two detection rates.

Screen - to test or examine for the presence of something (a disease, for instance) (33).

Sensitivity - the chance of having a positive test result given that you have a disease (not to be confused with *positive predictive value [PPV]*, which is the other way around) (35).

Specificity - the chance of having a negative test result given that you do not have a disease (not to be confused with *negative predictive value [NPV]*, which is the other way around) (35).

Squamous cell carcinoma - a carcinoma that is made up of or arises from squamous cells. Squamous cells are made up of or derived from squamous epithelium (33).

Squamous intraepithelial lesion (SIL) - dysplasia that is seen on a Pap smear. These changes may be graded as:

- Low-grade (LSIL)
- High-grade (HSIL)
- Possibly cancerous (malignant) (33)

Systematic review - a review in which specified and appropriate methods have been used to identify, appraise, and summarize studies addressing a defined question. It can, but need not, involve meta-analysis (35).

Triage - the sorting of patients (as in an emergency room) according to the urgency of their need for care (33).

Commonly used Acronyms

PEBC	Program in Evidence-based Care
CIN	Cervical Intraepithelial Neoplasia
CCO	Cancer Care Ontario
HPV	Human Papillomavirus
LBC	Liquid-based Cytology
OCSP	Ontario Cervical Screening Program
SIL	Squamous Intraepithelial Lesion

Appendix 3. Recommended management for women with abnormal cytology (i.e., appendix to the Interim Recommendations).

ASCUS (Atypical squamous cells of uncertain significance)

- HPV DNA testing with cytology is recommended for women aged 30 or older with ASCUS (C-III).
 - If the HPV DNA test is positive, women should be referred for colposcopy. If the HPV DNA test is negative, women should have repeat cytology in 12 months. Once a woman has had two negative cytology test results, she should return to routine screening.
 - In the absence of HPV DNA testing, a repeat Pap test in six months is acceptable. If the Pap test is abnormal, women should be referred for colposcopy. If the Pap test is negative, women should have repeat cytology in another six months. Once a woman has had two negative Pap tests results, she should return to routine screening.
- In women under the age of 30, a repeat Pap test in six months is recommended (C-III).
 - If the Pap test is abnormal, women should be referred for colposcopy. If the Pap test is negative, women should have repeat cytology in another six months. Once a woman has had two negative Pap tests results, she should return to routine screening.
- Referral to colposcopy, without HPV DNA testing or repeat cytology, is only recommended in situations where there is a high probability of patient loss to follow up, or if there are other symptoms suggesting cervical abnormality (e.g., abnormal bleeding) (A-I).

ASC-H (Atypical squamous cells: cannot exclude high grade squamous)

- Colposcopy is recommended for women with ASC-H (A-II).

LSIL (Low-grade squamous intraepithelial lesion)

- Either colposcopy or repeat cytology in six months is recommended for women with LSIL (B-II).
 - If repeat cytology is used and the Pap test is abnormal, women should be referred for colposcopy. If the Pap test is negative, women should have repeat cytology in another six months. Once a woman has had two negative Pap test results, she should return to routine screening.
 - There is limited evidence to support the use of intravaginal estrogen to reverse the cytologic changes in postmenopausal women with LSIL. A course of intravaginal estrogen followed by repeat cytology approximately a week after completing the regimen is acceptable for women with LSIL who have clinical or cytological evidence of atrophy and no contraindications to using intravaginal estrogen. Referral for colposcopy is recommended if a result of ASC-US or greater is obtained (CIII).

HSIL (High-grade squamous intraepithelial lesion),

- Colposcopy is recommended for women with HSIL (A-II).

AGC (Atypical glandular cells)

- Colposcopy is recommended for women with AGC (A-II).
- Women with AGC should also receive endocervical and endometrial sampling, where appropriate (A-II).

Qualifying Statements

- These are minimum guidelines only. Certain clinical situations may require earlier follow-up/referral for colposcopy.
- Repeat Pap test should not be performed earlier than three months following the original.
- Pap test should not be used as the sole assessment of a visible cervical lesion. These patients require biopsy for accurate diagnosis.

Key Evidence

Seven practice guidelines, six technology assessments, one meeting press release, one systematic review, three randomized controlled trials, one meta-analysis, eight cross-sectional studies, one prospective cohort study, four case-control studies, seven retrospective studies, and one conference report form the evidence for this practice guideline. If the evidence-base for these recommendations is required, please email ccopgi@mcmaster.ca.

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