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Evidence-based Series: Section 1

Cervical Screening: A Clinical Practice Guideline

C.M. McLachlin, V. Mai, J. Murphy, M. Fung Kee Fung, A. Chambers, and members of the Cervical Screening Guidelines Development Committee of the Ontario Cervical Screening Program and the Gynecology Cancer Disease Site Group of Cancer Care Ontario.

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)
Developed by the Gynecology Cancer Disease Site Group

Report Date: May 20, 2005

Questions

1. What is the optimal cervical screening tool (conventional cytology, liquid based cytology, or human papilloma virus [HPV] DNA testing)?
2. Do organized cervical screening programs with recall mechanisms reduce the incidence of and mortality due to cervical cancer compared to spontaneous cervical screening?
3. What is the most appropriate time for initiation and cessation of cervical screening?
4. At what time interval should women be screened?
5. Should women in special circumstances be screened (i.e., women who are pregnant, post-hysterectomy, or HIV-positive, adolescents, or women who have sex with women)?
6. What is the optimal management for women with abnormal cytology (up to but not including colposcopy/HPV management)?

Target Population

This practice guideline applies to all women who are, or have ever been, sexually active.

Recommendations

Please note that evidence ratings are in brackets. Please see the scale in Appendix 1.

Optimal Cervical Screening Tool

- Liquid-based cytology (LBC) is the preferred tool for cervical cytology screening (B-II). Conventional smear cytology remains an acceptable alternative (C-III).

Optimal Screening Circumstances

- Given the lower incidence and mortality associated with organized screening programs (with recall systems) elsewhere, a province-wide cervical screening program with an adequate recall mechanism is recommended (A-II).

Screening Initiation

- Cervical cytology screening should be initiated within three years of first vaginal sexual activity (i.e., vaginal intercourse, vaginal/oral and/or vaginal/digital sexual activity) (C-III).

Screening Interval

These recommendations do not apply to women who have had previous abnormal Pap tests. Please see the *Management of Women with Abnormal Cytology* section for further information.

- Screening should be done annually until there are three consecutive negative Pap tests (C-III).
- Screening should continue every two to three years after three annual negative Pap tests (B-II).
 - Screening at a three-year interval is recommended, supported by an adequate recall mechanism (B-II).
 - Women who have not been screened in more than five years should be screened annually until there are three consecutive negative Pap tests (C-III).

Screening Cessation

- Screening may be discontinued after the age of 70 if there is an adequate negative screening history in the previous 10 years (i.e. 3-4 negative tests) (B-II).

Screening Women with Special Circumstances

- Immunocompromised or HIV-positive women should receive annual screening (C-III).
 - Examples of situations where women may be immunocompromised include women who have received transplants and women who have undergone chemotherapy.
- Screening can be discontinued in women who have undergone total hysterectomy for benign causes with no history of cervical dysplasia or human papillomavirus (C-III).
 - 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 women who are not pregnant (B-III). Manufacturer's recommendations for the use of individual screening tools in pregnancy should be taken into consideration.
- Women who have sex with women should follow the same cervical screening regimen as women who have sex with men (B-II).

Recommended Management for Women with Abnormal Cytology

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 (abnormal bleeding, etc.) (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.

LBC versus Conventional Cytology

- Four technology assessments determined that LBC methodology was more sensitive than conventional cytology, while one technology assessment did not.
- Three technology assessments compared the rate of unsatisfactory specimens detected in LBC versus conventional cytology. All three assessments reported that there was a lower rate of unsatisfactory specimens with LBC compared to conventional cytology.

- Two technology assessments measured the safety of LBC compared to conventional cytology and both concluded that there were no additional risks associated with LBC than with conventional cytology.
- Two technology assessments compared HPV DNA testing to conventional cytology as a primary screening test. Neither assessment recommended routine HPV DNA testing as a primary screening test.

Optimal Screening Circumstances

- Six cross-sectional studies and one case-control study investigated either spontaneous cervical screening or organized screening programs. There were no studies identified that directly compared outcomes for women in spontaneous versus organized screening programs.
- The results of six of the seven studies supported the use of organized cervical screening programs over spontaneous screening. One cross-sectional study indicated that spontaneous cervical screening detected more cases of cervical cancer than organized screening; however, the conclusions of that study were based on crude detection rates for cervical cancer. When the results were adjusted for age and history of screening, organized cervical screening detected more cases of cervical cancer than spontaneous screening.

Screening Initiation, Interval and Cessation

- Five of the guidelines made recommendations regarding the age of initiation of screening (recommendations varied between 20 and 25 years). However, there were no comparative or non-comparative studies identified that addressed the issue of initiation of screening.
- Three guidelines made recommendations regarding screening cessation: two indicated that screening should not continue after age 70, and the other indicated that 65 years was an adequate age to cease screening (provided they have a history of negative tests).
- One cross-sectional study addressed screening cessation: they screened almost 700,000 women and determined that approximately five percent of the women between 50 and 69 years had HSIL compared to less than one percent of the women 70 years or older. Unfortunately, that study did not report rates of other cytological abnormalities (i.e. LSIL, ASCUS).
- All five guidelines recommended a screening interval of every two to three years for women 30 years of age or older. Two guidelines specified that women under 30 years should be screened annually (the other guidelines did not make age distinctions for their recommendation).
- One retrospective study that analyzed LBC or conventional cytology results of almost one million women determined that there was not an excessive risk of cancer in women screened every three years compared to women screened annually. Two case-control studies concluded that annual screening was necessary. It is important to note that the studies all included women who did not have a history of screening, which may bias results, because, without a history of screening, it is difficult to accurately assess the optimal screening interval.

Screening Women with Special Circumstances

- Only one guideline provided a recommendation for pregnant women: they indicated that pregnant women should follow the same screening routine as other women. There is no evidence to indicate that pregnant women should be screened any more or less frequently than women who are not pregnant.
- Three guidelines offered recommendations for women who are immunocompromised (HIV positive, transplant recipient); two guidelines recommended annual screening for those

women, and one guideline recommended more frequent screening for immunocompromised women than those who are not immunocompromised, but did not offer a timeline.

- Four guidelines recommended that women who had undergone hysterectomy for benign causes should discontinue screening.
- One guideline included in their recommendations women who had sex with women. The guideline recommended that those women follow the same screening routine as women who have sex with men. Three non-comparison studies were identified that also supported the recommendation that women who have sex with women should be screened routinely.

Management of Women with Abnormal Cytology

- Two practice guidelines specifically addressed the management of women with abnormal cytology. Both guidelines offered recommendations for women with various abnormal cytology results (ASCUS, ASC-H, LSIL, HSIL) based on extensive literature reviews.
- One randomized controlled trial compared the following three treatment arms: repeat cytology, HPV DNA testing, and immediate colposcopy in women with ASCUS or LSIL. The results supported HPV DNA testing for women with ASCUS and for women with LSIL, although some special circumstances exist.
- Further analysis of the above trial showed that, among women over 29 years with ASCUS, HPV DNA testing was much more sensitive in detecting CIN3 than conventional cytology, and resulted in fewer referrals for colposcopy.

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Appendix 1: Rating system for recommendations. ¹

Rating	Definition
<i>Scale for strength of recommendation</i>	
A	Good evidence for efficacy and substantial clinical benefit support recommendation for use
B	Moderate evidence for efficacy or only limited clinical benefit support recommendation for use
C	Evidence for efficacy is insufficient to support a recommendation for or against use, but recommendations may be made on other grounds
D	Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use
E	Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use
<i>Scale for quality of evidence</i>	
I	Evidence from at least 1 randomized controlled trial
II	Evidence from at least 1 clinical trial without randomization, from cohort or case-controlled analytic studies, or from multiple time series studies or dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

¹ Gross PA, Barrett TL, Dellinger EP, Krause PJ, Martone WJ, McGowan JE, Jr., et al. Purpose of quality standards for infectious diseases. *Clinical Infectious Diseases*. 1994;18:421.



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Evidence-based Series: Section 2

Cervical Screening: A Systematic Review

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4. At what time interval should women be screened?
5. Should women in special circumstances be screened (i.e., women who are pregnant, post-hysterectomy, or HIV-positive, adolescents, or women who have sex with women)?
6. What is the optimal management for women with abnormal cytology (up to but not including colposcopy/HPV management)?

INTRODUCTION

Although the incidence of cervical cancer has declined dramatically since the 1950s, an estimated 550 women in Ontario are diagnosed each year with cervical cancer, and 175 will die of their disease (1). Pap smear screening is well recognized as the major contributing factor in the decline in cervical cancer incidence. In Ontario, cervical cancer screening was largely delivered in an opportunistic model. However, the establishment of the Ontario Cervical Screening Collaborative Group and the Ontario Cervical Cancer Screening Program motivated reorganization of cervical screening delivery in order to improve the clinical effectiveness of the screening efforts.

At the same time, current understanding of the biology of cervical cancer, especially its relationship to the human papillomavirus (HPV), has focused research on cervical cancer prevention. Further technological advances have provided new techniques for cervical cell collection that attempt to improve the detection of cervical precursor lesions and provide a platform for HPV testing. The rapid evolution of these technologies and the proprietary nature of the available systems require an objective review of their clinical utility and resource implications in the Ontario cervical screening program.

Liquid-based cytology (LBC) provides a uniformly fixed and prepared sample of cervical cells, relatively free of artefacts and obscuring elements. By improving the presentation of the cells, the detection of cervical lesions will possibly be enhanced. LBC has undergone a rapid adoption in some sectors of Ontario laboratories; however, programmatic evaluations, including overall clinical and cost effectiveness, have not been previously undertaken.

HPV is a DNA virus that infects epithelial cells, especially those lining the lower genital tract. Epidemiologic, clinicopathologic, and molecular data have identified HPV as the major cause of cervical cancer (2). While over 80 different viral types have been identified, only a portion have been shown to regularly infect the genital tract. Genital HPV types are currently subdivided into low- and high-risk types according to their association with carcinoma (3). Despite the voluminous data accumulating on the relationship of HPV and cervical neoplasia, the clinical utility of HPV status is complicated by the variable natural history of the virus. HPV is a common infection that can be detected in up to 15% of the sexually active population, especially in women under the age of 30. However, many infections are transient, and only 7% of Ontario women show an abnormality on their Pap test (4). The challenge for cervical cancer prevention is to identify those women with HPV infections that result in high-grade lesions and cervical cancer while not overtreating those with infections that are likely to resolve.

HPV testing and LBC have been the focus of numerous studies and have produced new sets of recommendations in many countries (5-9). Guidelines have been released in the United States favouring the adoption of both new cytologic techniques and HPV testing (10,11). Health professionals in Ontario are faced with mounting pressure to provide those technologies; however, both the scientific merit and cost implications must be considered in the Ontario context. A recent Pan-Canadian conference examining cervical screening in Canada has drafted recommendations regarding new technologies (12). However, with the partial introduction of new technologies already occurring in this province, specific guidance is required on the optimal provision of cervical cancer screening.

In 1996, the Cervical Screening Collaborative Group developed interim guidelines for cervical cancer screening in Ontario. That process brought together an expert panel that drafted guidelines based on current practice. Currently, a more rigorous approach was necessary to properly examine the voluminous evidence on cervical cancer screening. That review of current evidence was a joint project of the Cervical Screening Program and the Practice Guidelines Initiative, Gynecology Cancer Disease Site Group (DSG) of Cancer Care Ontario.

Principles of Screening

Requirements of an Effective Screening Test

Certain requirements must be met for a screening test to be deemed effective (World Health Organization Criteria) (13). That is, to reduce mortality from the disease in question:

1. The condition should be an important health problem (significant prevalence and cause of mortality).
2. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
3. There should be a recognizable latent or early symptomatic stage in which treatment improves outcome.
4. There should be a suitable test or examination that is acceptable to the population.
5. There should be efficacious treatment for patients with recognized disease.
6. Facilities for diagnosis and treatment should be available.
7. There should be an agreed policy on whom to treat.
8. The screening program must be cost effective.
9. The screening tests should have a high sensitivity to detect disease (low false negative rate), a high specificity (low false positive rate), and high positive and negative predictive values.

The World Health Organization identified the above requirements plus six criteria for evaluating screening programs: validity, reliability, yield, cost, acceptance, and follow-up services (13). Validity refers to how well a screening test detects cervical abnormalities, and yield refers to the number of cervical abnormalities detected.

Current Cervical Screening Tests Available

Conventional cytology, where the clinician smears cervical cells on a glass slide and spray fixes the sample, has long been the backbone of cervical cancer prevention. Although that simple and inexpensive test is largely responsible for the dramatic decline in cervical cancer incidence, the technique is not without drawbacks. Currently in Ontario, approximately 0.5% of Pap tests are unsatisfactory due to inadequate sampling and preparation (4). Not only do those tests have to be repeated but also some unsatisfactory smears are the result of blood and inflammation obscuring significantly abnormal cells (14). Conventional smears also have a significant false negative rate due to sampling, preparation, screening and interpretative errors. Increasing expectations of cervical cytologic diagnosis techniques have led to efforts to improve the presentation of cervical cells provided by the conventional smear.

In LBC, the cervical sample is rinsed immediately in an aliquot of fixative and sent to the laboratory where the final slide is produced. Currently, two companies provide LBC preparation systems that are approved for use in Canada. The ThinPrep Pap Test (CYTYC, Boxborough, MA) uses a centrifugation filter technique, and the SurePath Pap Test (Tripath Care Technologies, Burlington, NC) uses a density gradient system. Both techniques provide a uniformly fixed and distributed sample of cells. However, both systems require proprietary sampling tools, fixatives, and preparation devices that are associated with a significant increase in cost per test as compared to the conventional smear. Both conventional and LBC samples are screened by cytotechnologists in a similar fashion.

Testing for HPV requires detecting HPV DNA within cervical cells, as the immunologic response to HPV is insufficient to allow informative antibody assays. Sensitive methods of HPV detection are available, including DNA hybridization and polymerase chain reaction. Currently, the one proprietary test that has Food and Drug Administration (FDA) approval has been the focus of most large studies evaluating HPV testing. Hybrid Capture 2 (HC2) (Digene Corporation, Gaithersburg, MD) uses a modified enzyme-linked immunoabsorbant (ELISA) assay to detect the DNA:RNA hybrids. As the major goal of cervical cancer screening is the detection of high-grade lesions of the cervix, the high-risk cocktail that detects the common oncogenic types of HPV has proven to be the most clinically useful. In fact, when HPV testing is referred to without reference to viral type, it is generally accepted that the high-risk cocktail is being used. Hybrid Capture can be performed on cervical samples collected using a specific swab or the test can be performed on the residual of cells of an LBC sample. That type of testing, often referred to as “reflex testing”, is more cost effective as a second sample is not necessary. Although HC2 currently is the most widely used method for HPV testing, other testing methods are being developed and must be evaluated when available.

METHODS

This systematic review was developed by Cancer Care Ontario's Program in Evidence-based Care (PEBC), using the methods of the Practice Guidelines Development Cycle (15). The review was initiated and supported by the Ontario Cervical Screening Collaborative Group, the Ontario Cervical Screening Program, and the PEBC's Gynecology Cancer DSG, with administrative support from the Ontario Medical Association Quality Management Program-Laboratory Services (QMP-LS). Evidence was selected and reviewed by the Cervical Screening Guidelines Development Committee, a collaborative group of stakeholders including gynecologists, family physicians, pathologists, and members of the PEBC's Gynecology Cancer DSG.

The systematic review and companion guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Literature Search Strategy

The MEDLINE (1998 to July 2004), EMBASE (1998 to July 2004), and Cochrane Library (2004, Issue 2) databases were searched for practice guidelines, technology assessments, systematic reviews, and clinical trials. Reference lists of papers and review articles were scanned for additional citations. The Canadian Medical Association Infobase, the National Guidelines Clearinghouse, and other Web sites were searched for existing evidence-based practice guidelines.

The following text words and medical subject headings (MeSH) were used: cervix, cervical, cancer, carcinoma, screening, and mass screening (as an exploded MeSH term). Search terms related to study design and publication type, used to search the MEDLINE and EMBASE databases, included clinical trial (text word and publication type), clinical trials (as an exploded MeSH term), meta-analysis (text word and publication type), and systematic review.

Inclusion Criteria

Table 1 describes the details of the inclusion criteria and outcome variables for each question addressed in this practice guideline.

Table 1. Details of inclusion criteria.

Question	Inclusion Criteria	Outcomes
1. What is the optimal cervical screening tool?	<ul style="list-style-type: none"> Practice guidelines, systematic reviews, technology assessments comparing conventional cytology to liquid-based cytology or to HPV DNA testing. Practice guidelines, systematic reviews, technology assessments, RCTs, prospective and retrospective cohort studies comparing various LBC methodologies 	<ul style="list-style-type: none"> Sensitivity, specificity of the intervention Rates of unsatisfactory specimens Safety/adverse effects of the intervention
2. Do organized cervical screening programs with recall mechanisms reduce the incidence of and mortality due to cervical cancer?	<ul style="list-style-type: none"> Practice guidelines, systematic reviews, technology assessments, prospective and retrospective cohort studies comparing organized cervical screening programs to spontaneous cervical screening. 	<ul style="list-style-type: none"> Rates of detection of abnormal cytology Mortality due to cervical cancer
3. What is the most appropriate time for initiation and cessation of cervical screening?	<ul style="list-style-type: none"> Practice guidelines, systematic reviews, technology assessments, RCTs, prospective and retrospective cohort studies identifying the most appropriate time for initiation and cessation of cervical screening. For the studies addressing cessation, results of cervical abnormalities had to be reported for women who had a negative screening history separately. 	<ul style="list-style-type: none"> Rates of detection of abnormal cytology
4. At what time interval should women be screened?	<ul style="list-style-type: none"> Practice guidelines, systematic reviews, technology assessments, prospective and retrospective cohort studies comparing time intervals for cervical screening. 	<ul style="list-style-type: none"> Rates of detection of abnormal cytology
5. Should women in special circumstances be screened?	<ul style="list-style-type: none"> Practice guidelines, systematic reviews, technology assessments, prospective and retrospective cohort studies describing cervical screening procedures for women in one of the following special circumstances: pregnant women, women post-hysterectomy, HIV positive women. 	<ul style="list-style-type: none"> Rates of detection of abnormal cytology Appropriateness of screening tool—reports sensitivity and specificity
6. What is the optimal management for women with abnormal cytology?	<ul style="list-style-type: none"> Practice guidelines, systematic reviews, technology assessments, meta-analyses, RCTs, describing management for women with abnormal cytology. Describe management for women at least up to but not necessarily including colposcopy/HPV management 	<ul style="list-style-type: none"> Rates of detection of cervical cancer

Note: HPV, human papilloma virus; LBC, liquid based cytology; RCT, randomized controlled trial

Exclusion Criteria

1. Abstracts, letters and editorials were not considered.
2. Papers published in a language other than English were not considered.

Methodology for Assessing the Cervical Screening Literature

Because cervical screening is an issue that affects all women, there have been a tremendous number of publications on the subject, including, in recent years, technology assessments and practice guidelines by other groups. The technology assessments provide a systematic overview of the current evidence available on a topic. The practice guidelines, on the other hand, are not entirely evidence-based; where there was limited evidence, consensus opinion was formed by the practice guideline authors. The authors of this practice guideline chose to review the recommendations and available evidence in the existing practice guidelines, in addition to reviewing comparative and non-comparative studies investigating a variety of aspects of cervical screening. This guideline presents all the recommendations of the existing guidelines and indicates throughout the text where those recommendations are consensus-based.

Synthesizing the Evidence

The results of the studies included in this guideline are described below. There were no statistical analyses performed on any of the data because there was either insufficient data to pool or meta-analyses had already been completed. The details of the meta-analyses are included in this guideline.

RESULTS

General

Literature Search Results

The literature search identified several published practice guidelines and technology assessments (5-11,16-20) eligible for inclusion in the guideline. The practice guidelines were either evidence- or consensus-based, depending on the available evidence (10,11,16-20). Where the practice guidelines made recommendations based on consensus, it is indicated throughout the *Results* section. In addition to the practice guidelines and technology assessments, a few comparative and non-comparative studies were identified that address various questions posed by this guideline. The included technology assessments, practice guidelines, and studies are listed in Table 2. In addition to the guidelines, there was one press release from a meeting of the International Agency for Research on Cancer (IARC) in May 2004 (21). The purpose of the meeting was to develop a consensus and evidence-based guideline about screening for cervical cancer. Because the guideline developed at the meeting has not been published yet, the press release information is described in this guideline.

Table 2. Literature research results.

Question		Studies (ref)
1. What is the optimal cervical screening tool?	Sensitivity and specificity a) conventional cytology versus LBC b) conventional cytology versus HPV DNA	6 technology assessments (5-9,22) 2 technology assessments (5,22)
	Rates of unsatisfactory specimens	3 technology assessments (5-7)
	Safety/adverse effects of the intervention	2 technology assessments (6,8)
	Comparison of LBC methodologies	1 technology assessment (5), 1 systematic review (23), 2 retrospective studies (24,25)
	Practice guideline recommendations	3 practice guidelines (10,11,16), 1 in press guideline (21)
2. Do organized cervical screening programs with recall mechanisms reduce the incidence of and mortality due to cervical cancer compared to spontaneous cervical screening?		6 cross-sectional studies (26-31), 1 case-control study (32)
3. What is the most appropriate time for initiation and cessation of cervical screening?		5 published guidelines (10,11,16,17,19) 1 in press guideline (21) 1 cross-sectional study (33)
4. At what time interval should women be screened?		5 published guidelines (10,11,16,17,19) 1 in press guideline (21), 1 retrospective cohort study (34), 2 case-control studies (35,36)
5. Should women in special circumstances be screened?		4 published guidelines (10,11,16,17), 1 in press guideline (21), 1 cross-sectional study (37), 1 prospective cohort study (38), 1 case-control study (39)
6. What is the optimal management for women with abnormal cytology ?		2 published guidelines (18,20) , 3 RCT (40-42), 1 meta-analysis (43), 4 retrospective studies (44-47), 1 conference report (12)

Note: LBC, liquid based cytology; RCT, randomized controlled trial

Seven published guidelines with recommendations on cervical screening were identified (10,11,16-20). The Cervical Screening Guidelines Development Committee applied the Appraisal of Guidelines Research and Evaluation instrument (AGREE), a rating system for guidelines, to the seven guidelines (Table 3). Four members of the Committee independently reviewed and applied the AGREE instrument to each of the guidelines. The average score was calculated for each question. The guidelines scored consistently well on several AGREE criteria, including guideline development from a variety of professional stakeholders and making specific and unambiguous recommendations. There were some differences in the development and presentation of the guidelines. Five guidelines (10,11,16,18,20) clearly outlined their systematic methodology for collecting data, and two guidelines (17,19) did not.

Table 3. AGREE rating for cervical screening guidelines (48).

Guideline	ACOG 2003 (16)	ACS 2002 (11)	USPSTF, 2002 (10)	NZGG 1998 (17)	CTFPHE, 1994 (19)	ASCCP 2001 (18)	NHMRC, 2004 (20)
Overall objectives are described	Disagree	Agree	Strongly agree	Agree	Disagree	Strongly agree	Agree
Clinical questions are described	Disagree	Disagree	Disagree	Disagree	Disagree	Disagree	Agree
Patient population is described	Agree	Agree	Agree	Agree	Agree	Strongly agree	Agree
Guideline group represents individuals from professional groups	Agree	Agree	Strongly agree	Agree	Agree	Strongly agree	Strongly agree
Patients views and preferences have been sought	Disagree	Disagree	Disagree	Disagree	Disagree	Disagree	Disagree
Target users of the guideline are identified	Strongly agree	Agree	Agree	Agree	Disagree	Agree	Agree
Guideline piloted among targeted users	Disagree	Disagree	Disagree	Disagree	Disagree	Disagree	Strongly agree
Systematic methods used to search for evidence	Strongly agree	Strongly agree	Strongly agree	Disagree	Disagree	Strongly agree	Strongly agree
Criteria for selecting the evidence are clearly described	Disagree	Agree	Strongly agree	Disagree	Disagree	Strongly agree	Strongly agree
Methods for formulating recommendations clearly described	Disagree	Agree	Agree	Disagree	Disagree	Agree	Agree
Health benefits and risks have been considered in recommendations	Agree	Agree	Agree	Agree	Agree	Agree	Agree
Recommendations and supporting evidence are linked	Strongly agree	Strongly agree	Strongly agree	Agree	Agree	Agree	Agree
Guideline externally reviewed by experts prior to publication	Disagree	Disagree	Agree	Disagree	Disagree	Strongly agree	Strongly agree
A procedure for updating guideline is provided	Disagree	Disagree	Disagree	Agree	Disagree	Disagree	Agree
Recommendations are specific and unambiguous	Strongly agree	Strongly agree	Strongly agree	Strongly agree	Agree	Agree	Agree
Different options for management clearly presented	Agree	Agree	Agree	Agree	Disagree	Agree	Agree
Key recommendations easily identifiable	Agree	Agree	Strongly agree	Agree	Agree	Agree	Agree
Guideline is supported with tools for application	Disagree	Disagree	Disagree	Disagree	Disagree	Disagree	Disagree
Potential barriers in applying recommendations have been discussed	Disagree	Disagree	Disagree	Disagree	Disagree	Disagree	Disagree
Potential cost implications of the recommendations have been considered	Disagree	Disagree	Agree	Disagree	Disagree	Disagree	Disagree
Guideline presents key review criteria for monitoring	Agree	Agree	Agree	Agree	Disagree	Agree	Agree
Guideline is editorially independent from funding body	Agree	Agree	Agree	Agree	Agree	Agree	Agree
Conflicts of interest of guideline development members recorded	Disagree	Disagree	Disagree	Disagree	Disagree	Strongly agree	Disagree

Note: ACOG, American College of Obstetricians & Gynecologists; ACS, American Cancer Society; ASCCP, American Society of Colposcopy and Cervical Pathology; CTFPHE, Canadian Task Force on the Periodic Health Examination; NHMRC, National Health and Medical Research Council; NZGG, New Zealand Guidelines Group; USPSTF, United States Preventive Services Task Force.

Screening Tools

What is the Optimal Cervical Screening Tool?

Literature search results

Five high-quality, recent technology assessments comparing conventional cytology to LBC were identified for this practice guideline (5-9). Table 4 outlines the technology assessments included in the practice guideline. The National Institute of Clinical Excellence (NICE) technology assessment originally published in 2000 was updated in 2003 (49). One of the technology assessments identified that compared LBC to conventional cytology also compared HPV DNA testing to conventional cytology (5). In addition to that technology assessment, one other technology assessment by the National Health Services (NHS) Health Technology Assessment (HTA) program in the United Kingdom (UK) was identified that compared HPV DNA testing to conventional cytology (22).

Three practice guidelines (10,11,16) and the details of a cervical screening meeting (21) were also identified that provided recommendations for the use of LBC or HPV DNA testing as a primary cervical screening tool in relation to conventional cytology.

Sensitivity and specificity of conventional cytology versus LBC

Although most studies showed increases in sensitivity with the use of LBC when compared to conventional cytology, there are limitations to the study design in many reports. Many studies did not compare the test results to a gold standard reference (i.e., cervical histology) but used a concurrent or historical control group instead. That drawback is inevitable given the screening nature of the test and the fact that many women do not require histologic follow-up. However, results then must be interpreted cautiously. Table 4 outlines the sensitivity and specificity reported among the technology assessments for LBC and conventional cytology.

The technology assessment by the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) included 13 studies in their meta-analysis comparing LBC to conventional cytology (5). Eleven studies included enough information to be pooled in the meta-analysis for sensitivity. The sensitivity ranged between 53% and 96% for LBC and between 35% and 94% for conventional cytology. CCOHTA reported that the meta-analysis indicated an 11% improvement in sensitivity with LBC compared to conventional cytology (relative risk [RR], 1.11; 95% confidence interval [CI], 1.03–1.20; $p=0.01$). It is important to note, however, that the studies were quite heterogeneous ($p<0.00001$). There were four studies pooled to determine the overall specificity of LBC compared to conventional cytology. The specificity ranged from 45% to 100% for LBC and 17% to 100% for conventional cytology. The pooled results did not detect a significant difference between the specificity of LBC and conventional cytology (RR, 1.35; 95% CI, 0.82–2.23; $p=0.2$). Those results should be interpreted cautiously because the studies were significantly heterogeneous ($p<0.0001$).

The Institute for Clinical Systems Improvement (ICSI) technology assessment (6) did not report its own meta-analysis but reported the results from the meta-analysis conducted for the NICE technology assessment (7). The NICE technology assessment conducted a meta-analysis of 14 studies (split-sample studies, two-cohort studies, or cohort-control studies) that reported sensitivity and compared LBC to conventional cytology. They found that sensitivity with LBC was 8% greater than with conventional cytology (80% versus 72%, RR, 0.75; 95% CI, 0.59–0.96). In a meta-analysis of six studies that reported specificity for both LBC and conventional cytology, they reported that there was no difference in specificity between LBC and conventional cytology.

NICE recommended that LBC be used as the primary cervical screening test. The advantages they cited for LBC compared to conventional cytology were: LBC provides an improved method for slide preparation, thus producing more homogeneous samples than conventional cytology; LBC was consistently reported to be more sensitive than conventional cytology in the studies they reviewed; and the LBC method is more efficient in terms of handling

laboratory samples than conventional cytology. Even though NICE recommended LBC over conventional cytology, they were not able to recommend a specific LBC method among those that were examined (SurePath, ThinPrep, Cytoscreen, and Labonard Easy Prep).

The technology assessment conducted by the Agency for Health Care Policy and Research (AHCPR) (9) pooled studies that measured the sensitivity and specificity for conventional cytology. AHCPR reported a pooled specificity of 98% (95% CI, 97%–99%) and a pooled sensitivity of 51% (95% CI, 37%–66%). However, the studies were often biased because none of the studies had random sampling. Patients were more likely to be entered in studies if they had abnormal cytology. The proportion of women with abnormal cytology included in the studies ranged from 2% to 98%. The AHCPR assessment reported that as the prevalence of abnormal cytology increased, sensitivity increased and specificity decreased, which suggests that there is bias among the studies. If there were no bias, the prevalence of abnormal cytology would have no impact on sensitivity or specificity.

One of the five technology assessments identified did not support the use of LBC over conventional cytology. The technology assessment by the Medical Services Advisory Committee (MSAC) in Australia reported that there was insufficient high-quality data to indicate that LBC is better than conventional cytology in terms of its sensitivity and specificity to detect abnormal cytology (8). MSAC identified seven studies that compared conventional cytology to LBC; however, five of those studies did not compare the test results with a gold standard (i.e., cervical histology) and so were not included in their analysis. In the remaining two studies, the reported sensitivity for LBC and conventional cytology ranged from 42% to 83% and 39% to 90%, respectively, and the specificity ranged from 52% to 90% and 48% to 99%, respectively.

Unsatisfactory specimens

CCOHTA also conducted a meta-analysis comparing the rate of unsatisfactory specimens in LBC to the rate of unsatisfactory specimens in conventional cytology (5). They identified eight studies that compared LBC to conventional cytology and reported rates of unsatisfactory specimens that ranged from 0.1% to 1% for LBC and from 0.1% to 12% for conventional cytology. The meta-analysis detected a lower rate of unsatisfactory specimens in LBC compared to conventional cytology (RR, 0.34; 95% CI, 0.20–0.59; $p=0.0001$) (Table 4). Note that there was statistically significant heterogeneity among the studies included in the meta-analysis ($p<0.00001$).

ICSI identified 11 studies that compared LBC and conventional cytology in terms of unsatisfactory specimen rates (6). Eight of those studies reported fewer unsatisfactory specimens in LBC than in conventional cytology. The rate of unsatisfactory specimens ranged between 2% and 24% for LBC and 2% to 39% for conventional cytology. The NICE technology assessment identified 35 studies that compared LBC to conventional cytology and reported unsatisfactory specimen rates (7). NICE found that the unsatisfactory specimen rates ranged from 0% to 8.5% for LBC and from 0% to 17.4% for conventional cytology. Neither ICSI nor NICE reported pooled the unsatisfactory specimens results.

Safety/Adverse effects of conventional cytology versus LBC

The MSAC technology assessment (8) reported that the risks associated with LBC were similar to those associated with conventional cytology but that there were no additional risks with LBC. The ICSI technology assessment (6) also noted that there were no known contraindications to LBC that were different for conventional cytology. ICSI reported that there was no evidence comparing morbidity rate between LBC and conventional cytology. In addition, no evidence was identified for mortality rates in the studies. The ICSI technology assessment stressed that clinicians need to be properly trained to use any cervical screening tool in order to maintain accuracy of results and safety of patients.

Guideline recommendations for conventional cytology versus LBC

The ACOG (American College of Obstetricians and Gynecologists) guideline indicated that either method of cervical screening (conventional cytology versus LBC) was acceptable (16). ACOG based that recommendation on the technology assessment by AHCP (9). Interestingly, the American Cancer Society (ACS) also recommended either screening test; however, the ACS guidelines indicate that women under 30 who undergo screening with LBC only require screening every two years as opposed to annually (11). ACS based their recommendation on a review of individual studies but did not pool the individual study results. ACOG did not make the recommendation according to age because they reported that there was not enough evidence at that time to support bi-annual screening in women under 30 years. The United States Preventive Services Task Force (USPSTF) indicated that there was insufficient evidence to support or refute the use of LBC instead of conventional cytology for cervical screening (10). The USPSTF stated that there were not enough studies comparing LBC against a reference standard (colposcopy or histology) to make a recommendation.

In 2004, an IARC press release described the recommendations that they derived through the consensus of the committee members (21). They did not indicate that LBC was preferred over conventional cytology. They stressed that any screening methodology should be evaluated based on local feasibility, cost, and long-term impact on invasive cancer. Their recommendations for screening interval and initiation were the same for both LBC and conventional cytology (every three years for women between the ages of 25 and 49, every five years for women over 50). However, the IARC meeting minutes provided no references to support their recommendation.

Comparison of LBC methodologies

A variety of LBC methodologies have been developed; however, the two methodologies most widely studied are ThinPrep (Cytoc Corp., Boxborough, MA) and SurePath (previously known as AutoCyte; TriPath Imaging, Burlington, NC). The ThinPrep and SurePath tests are both currently used in Ontario. One systematic review (23) and one technology assessment (5) were identified that analyzed the LBC methods by comparing the results of ThinPrep versus conventional cytology to the results of SurePath versus conventional cytology. No studies were identified that directly compared the two LBC methodologies. The systematic review literature search covered 1995 to April 30, 2000, and the technology assessment literature search covered 1997 to July 2003. Two additional studies published after the technology assessment were identified that compared ThinPrep to conventional cytology (24,25), and an Ontario evaluation of SurePath has recently been published (50).

The CCOHTA technology assessment included 13 studies in their meta-analysis comparing LBC to conventional cytology (5). Eight studies compared ThinPrep to conventional cytology, and five studies compared SurePath to conventional cytology. CCOHTA compared ThinPrep to SurePath by examining the rate of unsatisfactory specimens. Four of the ThinPrep studies and four of the SurePath studies reported unsatisfactory specimen rates. A meta-analysis of the ThinPrep versus conventional cytology studies found no significant difference in the unsatisfactory specimen rate between ThinPrep and conventional cytology (RR, 0.62; 95% CI, 0.25–1.57; $p=0.3$). A meta-analysis of the SurePath versus conventional cytology studies detected a significant decrease in the number of unsatisfactory specimens among the SurePath tests compared to conventional cytology (RR, 0.20; 95% CI, 0.09-0.47; $p=0.0002$). It is important to note that both meta-analyses had significant heterogeneity ($p<0.001$).

The systematic review by Klinkhamer et al (23) identified 10 studies between 1995 and April 30, 2000 that compared either ThinPrep or SurePath tests to conventional cytology. Four studies compared SurePath to conventional cytology, and six studies compared ThinPrep to conventional cytology. The systematic review did not conduct a meta-analysis of the studies but provided a summary of each study instead. They concluded that there was insufficient evidence

among the SurePath studies to indicate that SurePath tests detected more cervical abnormalities than did conventional cytology and that further studies were necessary. The systematic review concluded that ThinPrep was more sensitive than and equally as specific as conventional cytology in detecting cervical abnormalities.

As mentioned previously, two additional studies published since the CCOHTA technology assessment have been identified that compared ThinPrep to conventional cytology. Renshaw et al (24) included ThinPrep and conventional cytology slides that were reviewed up to five times each. Overall there were 89,815 interpretations of conventional cytology slides and 20,886 interpretations of ThinPrep slides. ThinPrep had significantly fewer false-positive (1.6%) and false-negative (1.3%) rates than conventional cytology (3.2% and 2.1%, respectively; $p < 0.05$).

In the study by Cheung et al (25), 191,581 conventional cytology tests were compared to 190,667 ThinPrep tests. They reported that the unsatisfactory rate was lower for ThinPrep than for conventional cytology (0.32% versus 0.48%) and that there were fewer suboptimal cases with ThinPrep than with conventional cytology (12.97% versus 19.12%).

The Ontario review of SurePath (50) included over 350,000 specimens compared to a similar sized historical control. The unsatisfactory rate was reduced by over 50%. The study also noted increased detection of all squamous abnormalities, especially LSIL.

HPV DNA testing

Two technology assessments were identified that compared HPV testing as a primary screening tool to conventional cytology (5,22). CCOHTA reported the results of an extensive systematic review specifically comparing HPV DNA testing methodologies to conventional cytology (5). They identified 12 studies that reported on HPV DNA testing alone as a primary screening test compared to conventional cytology. The reported overall sensitivity ranged from 68% to 100% for HPV DNA testing, and the sensitivity ranged from 20% to 89% for conventional cytology. The overall specificity was lower for HPV DNA testing (range 16% to 97%) compared to conventional cytology (range 87% to 99%) (Table 4). Each of the 11 studies that reported specificity indicated that specificity was lower for HPV DNA testing than for conventional cytology.

In 1999, the NHS HTA programme reported a technology assessment comparing HPV DNA testing methodologies with conventional cytology (22). The objective was to establish the role of HPV DNA testing in cervical screening, to determine the most appropriate method of HPV DNA testing, and to identify any gaps in the current literature in terms of HPV DNA testing and cervical screening. They reported that HPV DNA testing was more sensitive in detecting high-grade CIN than conventional cytology but that HPV DNA testing has lower specificity than conventional cytology (especially in younger women). The NHS HTA recommended that widespread use of HPV DNA testing was not appropriate at this time due to the concern regarding specificity; however, they did suggest that women with a history of abnormal cytology (borderline cytology smears) might benefit from HPV DNA testing because of its high sensitivity. No pooled sensitivity or specificity values were reported because that report reviewed a wide variety of HPV DNA testing methods.

Guideline recommendations for conventional cytology versus HPV DNA testing

The ACOG described HPV DNA testing in their guideline and acknowledged that HPV DNA testing in addition to conventional cytology increased sensitivity, although it decreased specificity (16). The ACOG indicated that, at that time, routine screening with conventional cytology alone was acceptable. The ACOG derived their recommendation on the use of HPV DNA testing from the systematic review in the practice guideline by the ASCCP (American Society of Colposcopy and Cervical Pathology) (18). If the HPV DNA test was going to be used, the ACOG recommended that women over 30 years being screened using cervical cytology

testing alone should have negative results on three annual tests before reducing their screening schedule to every two to three years. However, women over 30 years who receive a combination of a cervical cytology test and HPV DNA testing require negative results (on both tests) on one annual screening to reduce screening frequency to every three years. If either of the tests shows abnormal results, then more frequent screening is required (51). That recommendation was based on limited evidence. The rationale behind recommending that only women over 30 years be screened using HPV DNA testing stemmed from evidence that indicated that the specificity of HPV DNA testing was higher for women over 30 years old. The ACS suggested that the specificity was higher in the women over 30 years because viral infections are less common and are less likely to be of a 'transient nature' among the older age group.

The ACS made the same recommendation as ACOG; however, at the time the ACS guidelines were published, the HPV DNA test was not FDA approved. Therefore, their recommendation was conditional upon FDA approval. The ACS also indicated that if HPV DNA testing was to become part of routine screening, then there should be more education and counselling available for women. For instance, if a woman were to undergo both HPV DNA testing and conventional cytology and her cytology was negative, but she had a positive high-risk HPV result, she would need to be educated regarding those conflicting results.

The USPSTF guideline indicated that "adding HPV DNA testing to conventional screening is unlikely to be worthwhile" (10). The guideline did report that HPV DNA testing might have a role in primary screening if it were able to distinguish high-risk women from low-risk women, because screening schedules could be tailored based on risk. The USPSTF guidelines indicated that several trials were currently underway that would hopefully provide some clarity regarding the efficacy of HPV DNA testing as a primary cervical screening test.

The IARC indicated that HPV DNA testing was an option for screening women, and its use depended upon local circumstances, cost, and acceptability of the test (21). They recommended that, if HPV DNA testing was implemented, there should be a longer interval between screens (they did not indicate the length), and only women over 30 years should be screened using HPV DNA testing. Table 5 provides an overview of the recommendations of those practice guidelines.

The Pan Canadian conference on Cervical Cancer Prevention recommended the use of LBC as the preferred method for cervical cytology screening (12).

Table 4. Outcomes reported in the technology assessments addressing the optimal screening tool

HTA	# of studies (type of study)	Comparison	Sensitivity	Specificity	Unsatisfactory specimens	Comments regarding the quality of the literature	Recommendations
CCOHTA 2003 (5)	13 (10 split-sample, 3 two-cohort)	LBC versus CC	LBC 53%-96% CC 34.5%-94% Pooled data: LBC has 11% improvement in sensitivity over CC (RR 1.11 95% CI 1.03-1.20)	LBC 45%-99.5% CC 17%-99.7% Pooled data: no difference in specificity between LBC and CC	LBC 0.1%-1% CC 0.1%-12% Pooled data: LBC has lower rate of unsatisfactory specimens than CC (RR 0.34 95% CI 0.20-0.59)	Recommendations and conclusions based on independently controlled trials and meta-analyses. RCTs with cervical cancer as the endpoint will likely never be conducted because of the sample size required, prolonged follow-up and ethical issues.	<ol style="list-style-type: none"> 1. Pap testing using LBC is clinically effective in that it offers superior sensitivity and lower unsatisfactory rates than CC. 2. LBC is the most appropriate screening tool/technique for cervical screening. 3. There are significant incremental costs to the adoption of LBC by itself—LBC may be cost-effective if other measures are considered and undertaken by the screening program. 4. HPV DNA testing, alone or with cytology, is more sensitive than CC, but less specific.
		High versus normal risk	LBC is more sensitive than CC in normal risk (RR 1.17 (95%CI 1.02-1.35). No difference in sensitivity between LBC and CC in high risk (RR 1.07 95% CI 0.97-1.18).	No difference in specificity between LBC and CC in normal risk (RR1.00 95% CI 0.98-1.02) or high risk (RR 1.19 95% CI 0.96-1.47)	NR		
	12 (not specified)	HPV DNA testing versus CC	ASCUS: HPV DNA testing 88-98%; CC 42-78% LSIL: HPV DNA testing 68-95%; CC 20-89% HSIL: HPV DNA testing 96-100%; CC 60-86%	ASCUS: HPV DNA testing 89-96%; CC 94-98% LSIL: HPV DNA testing 61-97%; CC 87-99% HSIL: HPV DNA testing 16-87%; CC 89-99%	NR		
ICSI, 2003 (6)	25 (17 split-sample, 8 two-cohort)	LBC versus CC	Reported the results of the meta-analyses performed by NICE (7).		LBC 2-24% CC 2-39%	To date there are no RCTs available reporting clinical outcomes (incidence of invasive cancer or cancer mortality).	<ol style="list-style-type: none"> 1. LBC is an option for cervical cancer screening. <ul style="list-style-type: none"> • For pre-invasive cervical lesions, LBC is comparable to CC. • For minor grade lesions: higher detection rate with LBC than CC. • LBC has no impact on the safety of the patient compared to CC.
NICE, 2003 (49) 2000 (7)	14 (split-sample, two-cohort—number of each not specified)	LBC versus CC	Pooled data: LBC has a 12% improvement in sensitivity over CC (RR not reported)	Pooled data: no difference in specificity between LBC and CC (RR not reported)	LBC 0-8.5% CC 0-17.4%	There are no RCTs available reporting clinical outcomes (incidence of invasive cancer or cancer mortality). Most of the data available are split-sample studies.	<ol style="list-style-type: none"> 1. LBC should be used as the primary means of cervical screening. 2. There is insufficient evidence to recommend one LBC product over another.
		High versus normal risk	LBC has a 4.9% improvement in women at normal risk, and 2.8% for women at high risk (RR not reported)				

HTA	# of studies (type of study)	Comparison	Sensitivity	Specificity	Unsatisfactory specimens	Comments regarding the quality of the literature	Recommendations
MSAC, 2002 (8)	7 (not specified)	LBC versus CC	LBC 42%- 83% CC 39%- 90%,	LBC 52%-90% CC 48%- 99%	NR	"There are problems associated with the calculation of sensitivity and specificity for all of the published primary studies investigating LBC."	There is a lack of evidence to support the use of LBC over CC.
AHCPR, 1999 (9)	25 (not specified)	LBC versus CC	There is substantial uncertainty about LBC –no pooled results reported. CC 51% (95% CI 37%-66%)	There is substantial uncertainty about LBC –no pooled results reported. CC 98% (95% CI 97%-99%)	NR	There are no RCTs available. There are a lot of studies available, however, many are biased. Mostly focus on CC.	LBC is more sensitive than CC.
NHS HTA, 1999 (22)	Not specified	HPV DNA testing versus CC	HPV DNA testing higher sensitivity than CC No pooled sensitivity values were reported because this report reviewed a wide variety of HPV DNA testing methods.	HPV DNA testing lower specificity than CC No pooled sensitivity or specificity values were reported because this report reviewed a wide variety of HPV DNA testing methods.	NR	Eight databases were search resulting in 2100 studies. There are is a need for studies with 10,000 or more participants to address the accuracy of HPV DNA testing.	HPV DNA testing is more sensitive than CC, however, it has lower specificity than CC, especially among young women. HPV DNA testing is not recommended for widespread implementation (there may be certain situations where HPV is recommended over CC (i.e. older women where screening is problematic).

Note: AHCPR, Agency for Health Care Policy and Research; CC, conventional cytology (i.e. Pap smear); CCOHTA, Canadian Coordinating Office for Health Technology Assessment; CI, confidence interval; HTA, health technology assessment; ICSI, Institute for Clinical Systems Improvement; MSAC, Medical Services Advisory Committee; NHS HTA, National Health Services Health Technology Assessment; NICE, National Institute Clinical Excellence; NR, not reported.

Do Organized Cervical Screening Programs With Recall Mechanisms Reduce the Incidence of and Mortality due to Cervical Cancer Compared to Spontaneous Cervical Screening?

The advantages of an organized approach to cervical screening with monitoring, recall and follow-up seem intuitive. Unfortunately, no randomized trials were identified that compared organized cervical screening to spontaneous cervical screening. However, six cross-sectional studies (26-31) and one case-control study (32) were identified that studied organized cervical screening programs with recall mechanisms. For all of the studies, the recall interval was three to five years.

In 1988, the UK NHS implemented a cervical screening program with a three-year recall system: women were reminded every three years that they should be screened (52). Three identified studies compared the incidence of cervical cancer in the UK prior to 1988 and after 1988 (26,27,31). Most recently, Peto et al (31) reported the results of a study that specifically targeted women 20 to 35 years of age. They reported that cervical cancer mortality rose three-fold between 1967 and 1988 in that population of women. From 1983 to 1987, there were 605 deaths due to cervical cancer per 100,000 women in the UK between 20 and 35 years. From 1998 to 2002, there were 278 deaths due to cervical cancer per 100,000 women in the UK between 20 and 35 years. Thus, there were fewer than half as many deaths due to cervical cancer between 1998 and 2002 as there were between 1983 and 1987 in women of that age group.

In 1999, Quinn et al's cross-sectional study (26) analyzed the incidence and mortality of cervical cancer since 1950 in the UK. They found that 42% of women underwent cervical screening in 1988 (before the implementation of the screening program) compared to 85% in 1994. While there were 6.1 deaths due to cervical cancer per 100,000 women (across all ages) in 1987, the number of deaths dropped by almost half after the first 10 years of the cervical screening program: by 1997, there were 3.7 deaths due to cervical cancer per 100,000 women in the UK (26). Unfortunately, Quinn et al did not compare the organized screening program to spontaneous cervical screening. A similar cross-sectional study by Patnick also reported that mortality due to cervical cancer was decreasing in the UK faster than expected since the implementation of the organized screening program (27).

Nygaard et al's cross-sectional study from 2002 (29) evaluated the effectiveness of the screening program in Norway by comparing the incidence of cervical cancer before and after the implementation of the program. They analyzed the results of over four million Pap smears in 1.4 million women and reported that, since the initiation of the program in 1992, the incidence of cervical cancer had decreased by 22%.

A recent cross-sectional study by Adab et al (30) studied the effectiveness and efficiency of cervical screening in women who underwent spontaneous cervical screening. They estimated that 44% of sexually active women over the age of 20 years had been screened at least once, and one-third of the women had been screened two or more times. The study authors predicted that an organized screening program that aimed to screen at least 80% of the sexually active women over 20 years in Hong Kong would potentially reduce the number of new cases of cervical cancer by 46%.

The case-control study by Nieminen et al (32) compared 147 women with invasive cervical cancer to 1,098 healthy women. The women completed a questionnaire regarding their history of cervical screening. Nieminen et al calculated odds ratios (OR) for the incidence of cervical cancer by comparing women in organized screening programs to women who had never been screened, and women who underwent spontaneous screening to women who had never been screened. The authors found a significantly lower incidence of cervical cancer in women participating in organized cervical screening programs (OR, 0.38; 95% CI, 0.26–0.56) than in women who had never been screened. That difference still existed when the groups were adjusted for age and smoking. On the other hand, there was no significant difference in the incidence of cervical cancer between the women who underwent spontaneous cervical screening and those who had never been screened (OR, 0.82; 95% CI, 0.53–1.26).

In a cross-sectional study of cervical screening registry data, Bos et al concluded that organized cervical screening programs were not necessary; however, that study has some serious flaws (28). Although they reported that the crude detection rate of cervical abnormalities for spontaneous screening was higher than the crude detection rate for organized screening programs, they acknowledged that when they adjusted the rates for age and for women without a history of

screening, they found that there was a higher detection rate of cervical abnormalities for the organized screening program than for spontaneous screening. In order to accurately assess the effectiveness of organized screening programs compared to spontaneous screening, the study should only have included women with a history of screening. Women with no history of screening should not have been included, especially considering there was such a large disparity between women without a history of screening in the organized screening group (1%) compared to the spontaneous screening group (30%).

Screening Initiation, Frequency and Special Circumstances

Literature Search Results

Five guidelines (10,11,16,17,19) and the details of a cervical screening meeting (21) were identified that outlined cervical screening recommendations for women. A 2003 update (53) had been published for the ACS guideline released in 2002, and an additional news release (51) updated the ACOG Practice Bulletin. Table 5 compares the recommendations across the guidelines. In addition to the guidelines, a literature search was run to identify individual studies that addressed initiation, cessation, interval, or special circumstances. Seven additional studies were located: two cross-sectional (33,37), three case-control (36,39,54), one prospective cohort (38), and one retrospective cohort (34).

There was one press release from a meeting of the IARC in May 2004 (21). The purpose of the meeting was to develop a consensus and evidence-based guideline on screening for cervical cancer. Because the guideline developed at the meeting has not been published yet, the press release information is described in this guideline.

Table 5. Overview of recommendations for cervical screening from the published guidelines.

Guideline	LBC versus conventional cytology	HPV DNA testing ^a versus conventional cytology	Screening initiation	Screening cessation	Screening interval	Screening pregnant women	Screening women post-hysterectomy	Screening HIV positive women
IARC, 2004 (21)	Either method is acceptable	Either is acceptable for women over 30 years.	25 years	65 years	<ul style="list-style-type: none"> • Every 3 years for women 25-49 years • Every 5 years for women ≥50 	No comment	No comment	HIV positive women should be screened more frequently (specific interval not indicated)
ACOG, 2003 (16)	Either method is acceptable—there is no preferred method at this time.	>30 years—HPV may be used with conventional cytology or LBC (no more than every 3 years)	21 years (or 3 years after 1 st intercourse)	Not enough evidence to determine	<ul style="list-style-type: none"> • Annually for women <30 years • Every 2-3 years for women >30 years 	No comment	Hysterectomy for benign cause: discontinue screening	Women should be screened twice in the first year after diagnosis and annually thereafter.
ACS, 2002 (11)	LBC can be used instead of conventional cytology (LBC every 2 years in women <30 years, every 2-3 years in women >30)	>30 years—HPV may be used with conventional cytology or LBC (no more than every 3 years) ^b	21 years (or 3 years after 1 st intercourse)	70 years	<ul style="list-style-type: none"> • Annually for women <30 years^c • Every 2-3 years for women >30 years 	No comment	Hysterectomy for benign cause: discontinue screening	Women should be screened more frequently.
USPSTF, 2002 (10)	Insufficient evidence to support or refute the use of LBC	Insufficient evidence to support or refute the use of HPV DNA testing as a primary screening test	21 years (or 3 years after 1 st intercourse)	65 years	At least every 3 years	No comment	Hysterectomy for benign cause: discontinue screening	No comment
NZGG, 1998 (17)	No comment	No comment	20 years (for sexually active women)	70 years	Every 3 years	No change to usual recommendations	Hysterectomy for benign cause: discontinue screening	Immunocompromised women should be screened annually
CTFPHE, 1994 (19)	No comment	No comment	All sexually active women should be screened	No comment	Every 3 years (high risk women more frequently)	No comment	No comment	No comment

Note: ACOG, American College of Obstetricians & Gynecologists; ACS, American Cancer Society; CTFPHE, Canadian Task Force on the Periodic Health Examination; IARC, International Agency for Research on Cancer; NZGG, New Zealand Guidelines Group; USPSTF, United States Preventive Services Task Force.

^a HPV DNA testing for primary screening.

^b This recommendation is reasonable to consider if the FDA approves HPV DNA testing as a primary screening tool.

^c Women (<30 years) who have been screened with conventional cytology require annually screening, however, screening can be reduced to every two years in women (<30 years) who have been screened using liquid-based cytology.

What is the most appropriate time for initiation and cessation of cervical screening?

Initiation

No studies were identified in the literature search that addressed the optimal initiation of cervical screening. Several studies documented the incidence and prevalence of sexually transmitted diseases among adolescents and young women but did not address the issue of initiation of cervical screening (55,56).

Despite the lack of evidence, all the guidelines offered recommendations for the initiation of cervical screening. ACOG (16), ACS (11), and USPSTF (10) all recommend that cervical screening should start when a woman is 21 years old or three years after first intercourse, whichever comes first. The rationale for that recommendation was that invasive squamous cervical cancer takes several years to develop, and the risk of having a notable cervical lesion is small until three to five years after initial HPV exposure. The New Zealand Guidelines Group (NZGG) recommended that cervical screening should begin for sexually active women when they are 20-years old (17). The guidelines did not indicate when non-sexually active women should start screening. The Canadian Task Force guidelines recommend that all sexually active women should be screened but did not specify an age at which screening should commence (19). The IARC recommended that screening should not commence until women are 25 years old, stating that “there is minimal benefit and substantial harm in screening below age 25” (21).

Cessation

Five guidelines and one cross-sectional study addressed when cervical screening should cease. The ACOG recommendations did not specify at what age a woman should discontinue screening, because they did not feel that there was enough evidence to support a recommendation (16). The ACS (11) and NZGG (17), however, recommend that women discontinue screening at age 70 (provided the woman has had three consecutive negative tests over the past 10 years). The rationale that the ACS used to support that recommendation was that cervical cancer is rare in older women, especially women who have been screened previously. The ACS suggested that there might be more harms than benefits to screening older women, given the discomfort of the testing procedure and the potential for false-positive results. The USPSTF recommended discontinuing cervical screening in women at 65 years (10), citing the same rationale as ACS for discontinuing. However, the USPSTF acknowledged there is limited evidence to support the recommendation. The IARC recommended that women should cease screening at 65 years if they have always had negative screening results (21).

Colgan et al's cross-sectional study (33) compared the incidence of cervical disease between mature women (>50 years) and young women. Almost 700,000 women were included in their analysis. Over 60% of the mature women had no prior history of cervical screening, and results were reported separately for women who had never been screened and those who had. Of the 626 women who were diagnosed with HSIL and had a negative screening history, 5% were between the ages of 50 and 69 years. Less than 1% of the women who were diagnosed with HSIL were over 70 years. Unfortunately, the study did not provide details on the number of women with other cervical abnormalities according to age category.

At what time interval should women be screened?

Five guidelines (10,11,16,17,19), one retrospective cohort study (34), and two case-control (35,36) studies addressed the issue of the screening interval. Table 5 provides an overview of the recommendations of the guidelines.

A recent article by Sawaya et al (34) questioned whether a three-year interval between screenings was too long and led to a potential increase in the incidence of cervical cancer. In their retrospective study, they studied 938,576 women (aged 15-65 years) who participated in the Centre for Disease Control's (CDC) cervical screening program. Most of the women underwent conventional cytology tests; however, some women received LBC tests. In that study, the risk of

developing cervical cancer was 4 in 100,000 for annual screenings and nine in 100,000 for screening every three years in women less than 30 years old with three or more negative screening tests. The risk of developing cervical cancer was two in 100,000 with annual screenings and five in 100,000 for screening every three years in women between the ages of 30 and 44 years. In women 45 to 64 years, the risk of developing cervical cancer was 1 in 100,000 with annual screenings compared to two in 100,000 for women undergoing screening every three years. Sawaya et al concluded that the average excess risk of cervical cancer was three in 100,000 in women undergoing screening every three years. Based on those results, the CDC has modified their program from annual cervical screening to screening every three years.

The case-control study by Sasieni et al (36) matched 1,305 women with invasive cervical cancer to 2,532 healthy, age-matched controls. The RR of developing cervical cancer was calculated according to screening interval in three age categories: 20 to 39 years, 40 to 54 years, and 55 to 69 years. Sasieni et al estimated that, for women between 55 and 69 years, screening every five years would “prevent” 83% of incidences of cervical cancer and that screening annually would prevent 87% of cases. Among the women between 20 and 39 years, annual screening would prevent 76% of cancers, screening every three years would prevent 61% of cancers, and screening every five years would prevent 30% of the cervical cancers detected in that age group. For the women aged 40 to 54 years, annual screening would prevent 88% of cancers, and screening every three years would prevent 84% of cancers.

The case-control study by Miller et al (35) compared 482 women with invasive squamous cervical cancer to 934 healthy matched controls (matching based on age and race). Approximately 21% of the women with invasive squamous cervical cancer had been screened within a year compared to 52% of the healthy controls. Almost 32% of the women with invasive squamous cervical cancer had never been screened before compared to 10% of the women in the control group. They reported that the relative risk of cervical cancer was significantly higher in the women who were screened at two year intervals compared to annual screening (2.06, 95% CI 1.30-3.26, $p=.002$). There was not a significant difference in the relative risk of cervical cancer between two and three year intervals. This study included women over the age of 20; however, the study did not break down the relative risk according to age. In addition, it is important to recognize that one third of the women diagnosed with cervical cancer had never been screened before. In order to accurately assess screening intervals that study should have excluded women who had never been screened, and compare screening intervals and the risk of cervical cancer among the women who had been screened in the past.

The ACS recommended that women under 30 years old should be screened annually if using conventional cytology testing or every two years if using LBC (11). Women over 30 years who have had three consecutive negative tests should be screened every two to three years. The ACOG recommended that women over 30 years who are being screened using cervical cytology testing alone should have negative results on three annual tests before reducing the screening schedule to every two to three years (16). However, women over 30 years who receive a combination of a cervical cytology test and HPV DNA testing require negative results (on both tests) on one annual screening to reduce screening frequency to every three years. If either of the tests shows abnormal results, then more frequent screening is required (51). That recommendation is based on limited evidence.

The ACS made the same recommendation as ACOG; however, at the time of publication of the ACS guidelines, the HPV DNA test was not FDA approved. Therefore, their recommendation was conditional upon FDA approval.

The IARC recommended that women between the ages of 25 and 49 years be screened every three years, and that women 50 years or over undergo screening every five years (21). Those recommendations apply for women who are being screened with LBC or conventional cytology.

Special Circumstances

Should Women in Special Circumstances be Screened? (i.e., Women Who Are Pregnant , Post-Hysterectomy, or HIV-Positive, Adolescents, or Women Who Have Sex with Women)

Screening pregnant women

There were no studies identified that compared cervical cancer screening in pregnant women to non-pregnant women in terms of screening interval, safety of the screening test on the pregnancy and the rate of abnormal cytology detected.

The New Zealand Guidelines Group (NZGG) recommended that women who were pregnant or postnatal should follow the same screening regimen as other women (i.e. screening every three years for women with normal screens). The other guidelines did not comment on the cervical screening management of pregnant women.

Screening post-hysterectomy

There were no studies identified that compared cervical cancer screening in women with and without hysterectomies in terms of screening interval and the rate of abnormal cytology detected.

ACOG recommended that women who have had a hysterectomy with removal of the cervix for benign reasons could discontinue cervical screening. This recommendation is based on high quality evidence. They also recommended that women who have had a hysterectomy because of a history of CIN2 or CIN3 should be screened annually until they have three consecutive negative test results. ACOG acknowledged that this recommendation is based on limited evidence.

Similar to ACOG, the ACS recommended that women who have undergone a hysterectomy for benign reasons should discontinue screening. In addition, women with a history of CIN2 or CIN3, who have had a hysterectomy, should have three consecutive negative tests before screening is discontinued.

Screening HIV-positive women

There were no studies identified that attempted to define an optimal cervical screening strategy for HIV positive women. Four of the guidelines made recommendations for HIV positive women.

The ACOG guideline indicated that women with certain risk factors should be screened more frequently. Risk factors that ACOG identified were HIV positive women, women who are immunosuppressed (ex. after transplants) and women who were exposed to diethylstilbestrol in utero. According to ACOG, HIV positive women should be screened twice in the first year after diagnosis and annually thereafter. Despite indicating that more frequent screening was required for these higher risk women, the ACOG did not make recommendations as per frequency of screening to the women in the latter two risk scenarios listed.

The NZGG guideline recommended that women at higher risk for cervical cancer due to sexual behaviour, smoking, and contraceptive use do not require more frequent screening. Every three years is sufficient for these high risk women (17). However, women diagnosed with HIV or women who have had transplants do require more frequent screening. The NZGG guideline recommended annual screening for women with HIV or women who have had organ transplants.

The IARC recommended that HIV positive women should be screened more frequently than women who are not HIV positive (21). However, they did not indicate the interval that HIV positive women should be screened.

Screening adolescents

There have been several studies documenting the incidence and prevalence of sexually transmitted diseases among adolescents and young women (55,56), however, these studies do not address how adolescents should be screened.

In terms of adolescents, ACS recommended that even if a young woman does not require cervical cytology testing (i.e. is less than 21 years old and is not sexually active) it was important

to provide preventive health care to these women (health-risk assessment, sexually transmitted disease screening and treatment) (11). They stressed that the need for cervical screening should not be the basis for starting gynecologic care.

Screening women who have sex with women

The NZGG was the only guideline to make a recommendation specifically including women who have sex with women (17). They recommended that women who have had sexual intercourse should be screened, including women who have sex with women. Three studies were identified in the literature that addressed cervical screening among this population of women (37-39).

In the cross-sectional study by Bailey et al (37) 606 women who have sex with women were cervically screened. Approximately 80% of the women had heterosexual histories. Of the 606 women, 547 (90%) had negative cytology tests, and none of the women were diagnosed with invasive cancer. Among the women with heterosexual histories, 11% had abnormal cytology and among the women who did not have heterosexual histories, 5% had abnormal cytology. In the prospective cohort study by Marrazzo et al (38), 248 women who reported having sex with women were recruited and interviewed about their medical and sexual histories. Similar to the study by Bailey et al, 80% of the women included in this study reported having heterosexual histories. Twelve percent of the women who reported that they did not have a heterosexual history had abnormal cervical cytology compared to 10% of women with heterosexual histories. Unfortunately, neither of these studies compared the results to a control group of heterosexual women. The case-control study by Fethers et al (39) compared the cervical cytology of 356 women who indicated that they had sex with women to 286 women who reported that they had never had sex with women (controls). Among the women who had sex with women, 19% had abnormal cytology compared to 20% of the controls.

Management of Abnormal Cytology

What is the Optimal Management for Women with Abnormal Cytology (up to but not Including Colposcopy/HPV Management)?

Literature search results

Two practice guidelines (18,20), one conference report (12), one meta-analysis (43), one randomized controlled trial (41,42) and four retrospective studies (44-47) were identified that described the optimal management for women with abnormal cytology. The RCT, the ASCUS-LSIL Triage Study (ALTS), has been published in many separate articles (12,40-42,57-60).

Outcomes

The American Society of Colposcopy and Cervical Pathology (ASCCP) guidelines were developed in 2001 by a panel of 121 experts from 29 organizations (18). Extensive literature reviews were conducted to identify evidence on which to base recommendations. Where there was not enough evidence available, a consensus expert opinion was formed.

The ASCCP guidelines for the management of women with abnormal cytology are listed in Table 6. These guidelines recommend HPV triage for women with ASCUS and colposcopy for most other abnormalities. The ASCCP guidelines were thorough in that they considered the management of several 'special circumstances' including pregnancy, adolescence and menopausal status. Table 6 lists recommendations for the management of both postmenopausal and adolescent women. There is limited high-quality evidence available regarding the management of abnormal cytology in pregnant women, however, the ASCCP guidelines recommend that pregnant women with high-grade squamous intraepithelial lesions undergo colposcopy. In the absence of invasive disease pregnant women should undergo additional colposcopic and cytological examinations. It is important to note that the recommendations regarding the management of women in special circumstances are primarily based on expert opinion, rather than evidence.

Table 6. ASCCP Guidelines for women with abnormal cytology (18).

Condition	Management				
Women with ASCUS	Repeat cytology ^a	Negative test	Repeat cytology ^a	Negative test	Routine screening
		Positive test	Colposcopy	Positive test	Colposcopy
	HPV DNA testing ^b	Negative test		Repeat cytology (@ 12 months)	
		Positive test		Colposcopy	
	Colposcopy				
Post-menopausal women with ASCUS	Intravaginal estrogen therapy, then repeat cytology (1 week after estrogen therapy)	Negative test	Repeat cytology ^a	Negative test	Routine screening
		Positive test	Colposcopy	Positive test	Colposcopy
	Colposcopy or HPV DNA testing				
Women with ASC-H	Colposcopy				
Women with AGC	Colposcopy and endometrial sampling (if >35 years or abnormal bleeding)				
Women with LSIL	Colposcopy				
Post-menopausal women with LSIL ^c	Repeat cytology ^a (+/- intravaginal estrogen therapy ^d)	Negative test	Repeat cytology ^a	Negative test	Routine screening
		Positive test	Colposcopy	Positive test	Colposcopy
	HPV DNA testing	Negative test		Repeat cytology (@ 12 months)	
		Positive test		Colposcopy	
	Colposcopy				
Adolescent women with LSIL	Repeat cytology ^a	Negative test	Negative test	Routine screening	
		Positive test	Positive test	Colposcopy	
	HPV DNA testing ^b	Negative test		Repeat cytology (@ 12 months)	
		Positive test		Colposcopy	
	Colposcopy				
Women with HSIL	Colposcopy (with endocervical assessment)				

Note: AGC, atypical glandular cells; ASC-H, atypical squamous cells: cannot exclude high-grade squamous intraepithelial lesion; ASCUS, Atypical squamous cell of undetermined significance; HSIL, high-grade squamous intraepithelial lesions; LSIL, low-grade squamous intraepithelial lesions

^a Unless otherwise indicated, repeat cytology occurred after 4-6 months.

^b HPV DNA testing is preferred if liquid-based cytology is available.

^c Low risk, postmenopausal women with a history of negative screening.

^d Intravaginal estrogen therapy may be considered if there is clinical or cytological evidence of atrophy and no contraindications to estrogen therapy.

The National Health and Medical Research Council (NHMRC) guideline from Australia was originally published in 1994 and updated in 2004 (20). Like the ASCCP guideline, that guideline is very thorough and based on an extensive review of the literature. The

recommendations in the NHMRC guidelines are significantly different from the ASCCP, especially in the management of low-grade abnormalities:

- ASCCP recommends HPV triage for women with ASCUS and colposcopy for women with LSIL. The NHMRC recommends that women with ASCUS and LSIL receive repeat cytology screening after 12 months. The NHMRC did not support the use of HPV testing for managing cervical abnormalities.
- In the absence of HPV triage, ASCCP recommends colposcopy in women with two consecutive abnormal tests. The NHMRC recommends colposcopy in women with two consecutive abnormal tests in women over 30 years and recommends that women under 30 years should have three consecutive abnormal tests before colposcopy.
- ASCCP does not make specific recommendations regarding immunosuppressed women; the NHMRC recommends that immunosuppressed women be referred for colposcopy without additional cytology.

The Pan Canadian Conference on Cervical Cancer Prevention brought together a wide variety of stakeholders from across many disciplines in Canada to review evidence from the literature and published guidelines (12). Position papers on the provision of cervical cancer screening were drafted and extensively reviewed in a consensus process. Although the conference report did not provide overall management recommendations, it did review HPV testing in the triage of equivocal cytologic abnormalities. The consensus report recommended HPV testing for triage among women 30 years of age and over with an ASCUS Pap test.

In addition to the two practice guidelines identified, there was also a meta-analysis (43), one RCT (41,42), and four retrospective studies (44-47) eligible for inclusion in this practice guideline. Two other RCTs were identified and considered for inclusion; however, they did not report their results separately for ASCUS and LSIL (61,62).

The ALTS trial is the largest RCT to date comparing management options for women with abnormal cytology (41,42). The results of that study have been reported in a variety of articles (40-42,57-60). The main findings of this trial have been reported in two key articles: one targeting the patients with ASCUS (42), and the other describing the outcomes of the patients with LSIL (41) (Table 7). Women with ASCUS or LSIL were randomized to one of three management arms: immediate colposcopy, reflex HPV DNA testing or repeat conventional cytology. All of the women in the study were followed for two years, with semi-annual follow-up. At the end of the study, all women were to receive colposcopy. The reasoning for the colposcopy was two-fold: the researchers wanted to ensure patient safety, and they also wanted to “provide complete ascertainment of disease end points before a woman exited the study.” The ALTS trial did not provide data on the outcomes of the women after a CIN3 diagnosis. That is, they did not compare survival or incidence of invasive cervical cancer among the three management arms. However, the data from the ALTS trial may not be mature enough to provide these results.

It is important to note that, of the women included in the ALTS trial who were diagnosed with ASCUS in a community setting, only 32% of the women had ASCUS confirmed by clinical centre interpretations. In a follow-up study, Stoler et al (60) found that there was a lack of interobserver reproducibility of the cytology interpretations in the ALTS trial.

Among the women with ASCUS, the sensitivity of HPV DNA testing to detect CIN3 was 92.4% compared to 83.4% for conventional cytology (no p-value reported, confidence intervals do not overlap). The incidence of CIN3 was consistent across all three management arms (range 8.3%-9.3%); however, more incidences of CIN3 in the women in the HPV DNA testing arm were identified on the first visit compared to the conventional cytology arm (75.2% versus 40.7%, respectively).

The reflex HPV DNA testing arm was terminated early in the women with LSIL because 83% of the women were found to be HPV positive. That high percentage of HPV positivity does not provide sufficient clinical utility for HPV DNA testing as a triage test for LSIL. Based on limited data, among the women with LSIL, HPV DNA testing had a sensitivity of 95.2% to detect CIN3

compared to 72.8% for conventional cytology (no p-value reported, confidence intervals do not overlap). Similar to the ASCUS results, there was a consistent proportion of CIN3 detected across the three management arms (range 13.8%-18.3%), and more incidence of CIN3 were detected at the first visit in the women receiving HPV DNA testing compared to women with CIN3 receiving conventional cytology (68.3% versus 36.6%, respectively).

Table 7. Details of the ALTS trial comparing management options for women with abnormal cytology

Study	ALTS, 2003 (41,42)		
	Immediate colposcopy	HPV DNA testing	Conventional cytology
ASCUS			
Number of participants	1163	1161	1164
Sensitivity to detect CIN3	53.6% (43.2%-63.8%)	92.4% (88.7%-95.2%)	83.4% (78.7%-87.5%)
% of participants diagnosed with CIN3	8.3%	8.7%	9.3%
% of participants referred to colposcopy	100% (99.7%-100%)	53.1% (51.4%-54.8%)	58.1% (56.4%-59.8%)
LSIL			
Number of participants	673	224	675
Sensitivity to detect CIN3	55.9% (45.7%-65.7%)	95.2% (91.5%-97.6%)	72.8% (66.5%-78.5%)
% of participants diagnosed with CIN3	15.2%	18.3%	13.8%
% of participants referred to colposcopy	100% (99.4%-100.0%)	84.1% (82.2%-85.9%)	57.4% (54.8%-59.9%)

Note: ALTS, ASCUS-LSIL Triage Study; ASCUS, atypical squamous cells of uncertain significance; LSIL, low-grade **squamous intraepithelial lesion**

Sherman et al (58) re-analyzed the data from the ALTS trial according to age categories: 18 to 22 years, 23 to 28 years, and 29 years or older. Table 8 outlines the details of this study. They concluded that HPV DNA testing was much more sensitive in detecting CIN3 than conventional cytology, and resulted in fewer referrals for colposcopy among women over 29 years. They also concluded that neither HPV DNA testing nor conventional cytology provide useful triage in women with LSIL.

Table 8. ALTS trial results according to age (58)

Treatment arms		18-22 years	23-28 years	>29 years
ASCUS				
Number of participants with CIN3 (5.8% of total participants)		46	50	33
Sensitivity to detect CIN3 (95% CI)	Reflex HPV DNA testing ^a	97.8% (93.6-100.0)	96.0% (90.6-100.0)	93.9% (85.8-100.0)
	Conventional cytology	80.4% (69.0-91.9)	88.0% (79.0-97.0)	90.9% (81.1-100.0)
% of participants referred to colposcopy (95% CI)	Reflex HPV DNA testing ^a	71.0% (67.7-74.4)	65.2% (61.6-68.9)	31.2% (28.0-34.3)
	Conventional cytology	65.6% (62.1-69.1)	63.9% (60.2-67.5)	50.1% (46.7-53.5)
LSIL				
Number of participants with CIN3 (10.7% of total participants)		37	42	12
Sensitivity to detect CIN3 (95% CI)	Reflex HPV DNA testing ^a	100.0% (100.0-100.0)	97.6% (93.0-100.0)	83.3% (62.2-100.0)
	Conventional cytology	64.9% (49.5-80.2)	90.5% (81.6-99.4)	83.3% (62.2-100.0)
% of participants referred to colposcopy (95% CI)	Reflex HPV DNA testing ^a	86.7% (83.3-90.1)	88.0% (84.3-91.6)	74.7% (68.1-91.3)
	Conventional cytology	57.7% (52.8-62.7)	63.2% (57.7-68.7)	49.4% (41.8-57.0)

Note: ALTS, ASCUS-LSIL Triage Study; ASCUS, atypical squamous cells of uncertain significance; CI, confidence interval; CIN, cervical intraepithelial neoplasia; LSIL, low-grade **squamous intraepithelial lesion**

^a Cutpoint 1.0 pg/ml

A meta-analysis, published in 2004, included 15 studies that compared reflex HPV DNA testing to conventional cytology in the management of women with equivocal conventional cytology (i.e. Pap smear) results (43). The meta-analysis was not limited to RCTs, and, thus, included non-comparative studies. The ALTS trial (41,42) was included in the meta-analysis, and provided 42% of the patients in the analysis.

The pooled sensitivity of the reflex HPV DNA tests was 84.4% (95% CI, 77.6%-91.1%) and the pooled specificity was 72.9% (95% CI, 62.5%-83.3%). In the eight studies that used the Hybrid Capture II assay (type of HPV DNA test), the sensitivity and specificity were 94.8% (95% CI, 92.7%-96.9%) and 67.3% (95% CI 58.2%-76.4%), respectively.

The pooled sensitivity for conventional cytology at a diagnostic threshold of ASCUS to detect CIN3 was 81.8% (95% CI 73.5%-84.3%) and the specificity was 57.6% (95% CI, 49.5%-65.7%). The pooled sensitivity for conventional cytology at a diagnostic threshold of LSIL to detect CIN3 was 45.7% (95% CI, 34.0%-57.4%) and the specificity 89.1% (95% CI, 82.1%-96.2%).

The meta-analysis detected that the pooled ratio of the sensitivity to detect ASCUS with Hybrid Capture II assay compared to conventional cytology was 1.16 (95% CI, 1.04-1.29). For LSIL, the pooled ratio was 1.69 (95% CI, 1.54-1.85), and for HSIL the pooled ratio was 2.80 (95% CI, 2.43-3.31). In each situation, the Hybrid Capture II assay has significantly higher sensitivity than conventional cytology.

For specificity, the meta-analysis did not detect a significant difference in the detection of ASCUS between the Hybrid Capture II assay and conventional cytology. However, the specificity of the conventional cytology was significantly higher than Hybrid Capture II assay in the detection of LSIL and HSIL. It is important to note that the meta-analysis included a variety of reflex HPV DNA testing methodologies, and some of the patient data included in the meta-analysis was from non-comparative studies, so the results need to be interpreted cautiously.

Sherman et al (63) used the results of the ALTS study to compare women with HSIL, ASC-H or ASC-L. In the group of women undergoing HPV DNA testing, approximately 5% of the women with ASC-L were diagnosed with CIN3 or worse, compared to 24% of women with ASC-H

and 38% of women with HSIL. Among the group of women undergoing conventional cytology, 6% of the women with ASC-L were diagnosed with CIN3 or worse, compared to 17% of women with ASC-H and 29% of women with HSIL. Unfortunately, Sherman et al did not report the number of women in colposcopy group who were diagnosed with CIN3.

Two retrospective studies were identified that attempted to define the optimal management for women with atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (ASC-H) (44,45). The retrospective study by Selvaggi (44) identified 22 cases of ASC-H among 9214 Pap tests. Upon further investigation, 17 of the 22 cases were classified as LSIL (two cases) or HSIL (15 cases). Due to the high proportion of cases that are confirmed to be LSIL or HSIL (77%), Selvaggi et al recommended colposcopy for women with ASC-H. The retrospective study by Louro et al came to a similar conclusion (45). Louro et al studied the outcomes of 368 women with ASC-H. All of the women were followed up with LBC or conventional cytology six to 12 months after the ASC-H result. Upon follow-up 79% of women were found to have clinically significant lesions, 46% of the women had CIN2 or 3. Louro et al also subdivided their results according to age. They found that women less than 40 years were significantly more likely to have clinically significant lesions than women over 40 years (84% versus 66%, respectively, $p=0.01$). Louro et al concluded that women, regardless of age, should undergo colposcopy.

Two additional retrospective studies were identified that attempted to define the optimal management for women with atypical glandular cells (AGC) (46,47). Hammoud et al (46) found 189 women who had been diagnosed with AGC over a five year period at the University of Michigan Medical Center. There was histologic information for 114 of the women. Forty-eight percent of those women had significant histologic abnormalities, including endometrial cancer (11 women), invasive cervical cancer (five women), CIN3 lesions (23 women), and CIN2 lesions (10 women). Hammoud et al recommended that women should at least receive colposcopy upon a result of AGC. Chan et al reported similar outcomes in their retrospective study of 72 women with AGC (47). Forty-three percent of the women in their study had significant histologic abnormalities upon further investigation: including endometrial cancer (five women), invasive cervical cancer (11 women) and CIN lesions (14 women).

DISCUSSION

Cervical cytologic screening has been the single most successful cancer prevention tool in the last 40 years. However, given the largely opportunistic approach to screening, the ability to mount large, well-controlled studies of various screening practices is limited. Thus, there is limited high-quality evidence on which to base much of the current practice recommendations. Seven different groups have developed practice guidelines for cervical screening—all of the guidelines are based on some extent on expert or consensus opinion rather than evidence (10,11,16-20). When the Cervical Screening Program decided to update their practice guidelines, it was important that the guideline remain as true to the evidence as possible. For that reason, the guideline includes evidence from comparative and non-comparative studies, in addition to the recommendations of seven guidelines.

The optimal cervical screening regimen will undoubtedly change over time as technology develops and new evidence emerges. For that reason, the Cervical Screening Program acknowledges that the recommendations in this guideline will require review and revision. The Program in Evidence-based Care (PEBC) has a formal standardized procedure to ensure the currency of their guidelines. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

What is the Optimal Cervical Screening Tool (Conventional Cytology, Liquid Based Cytology, HPV DNA Testing)?

There is substantial evidence to support the use of LBC over conventional cytology in terms of satisfactory tests and sensitivity. The technology assessment by CCOHTA (5) established in their meta-analysis that LBC has an 11% improvement in sensitivity over conventional cytology. That technology assessment also reported that LBC has a lower rate of unsatisfactory specimens. Both of these factors have the potential to improve the efficiency and effectiveness of a screening system that is plagued by personnel and resource shortages.

The prime purpose of this guideline process was to weigh the clinical evidence and not to address the cost-effectiveness of one test over another. However, it is obvious that the introduction of LBC will lead to increased costs that will have to be balanced with other screening efficiencies. It is also recognized that the transition from conventional smear cytology to liquid based cytology may take time given the resources required for implementation and training. Although liquid based cytology is the preferred screening tool, conventional cytology remains an acceptable alternative.

The evidence supporting the use of HPV DNA testing as a primary screening tool as compared to conventional cytology indicates that HPV testing is more sensitive, but less specific than conventional cytology (5,22). The information regarding HPV screening continues to evolve but presently the two technology assessments that examined HPV testing indicated that it should not be routinely recommended as a primary screening test. In the future HPV screening, especially in women over the age of 30, may prove useful but further data in the Ontario context is needed.

Do Organized Cervical Screening Programs With Recall Mechanisms Reduce the Incidence of and Mortality due to Cervical Cancer Compared to Spontaneous Cervical Screening?

There is evidence to support the implementation of organized cervical screening programs with recall mechanisms to reduce the incidence of and mortality due to cervical cancer. In 1988, the NHS in the UK implemented an organized cervical screening program with a recall system. Since the implementation of the program they have significantly increased the number of women who are screened (42% in 1988 to 85% in 1994) (26). Also, the number of deaths due to cervical cancer in the UK dropped by almost half between 1988 and 1997 (26). A standardized Ontario provincial recall mechanism would be desirable and limited population based information has hampered the ability of these guidelines to reflect the specific needs of Ontario. However, the ability to provide this service is limited by health information privacy legislation. Nonetheless, the Ontario Cervical Screening Program remains committed to developing a recall system. Private practices and medical laboratories also have the potential to develop internal recall systems, especially in situations where there are stable patient populations.

What is the Most Appropriate Time for Initiation and Cessation of Cervical Screening?

Pap smear screening has evolved since the 1950s into a highly effective cancer prevention tool. However, this has occurred without randomized controlled trials and the benefit of this test is so evident that trials involving withholding the test are unethical. Therefore, there is little evidence in the literature to indicate the optimal timing for the initiation and cessation of cervical screening. Previous cervical screening guidelines have made recommendations for the initiation and cessation of screening based on limited evidence, previous practice and expert consensus.

The rationale behind the recommendation for the initiation of cervical screening is that HPV is a sexually transmitted virus and significant cervical lesions are unlikely to be detected until three to five years after initial HPV exposure and invasive squamous cervical cancer takes several years to develop. All but one of the guidelines indicated a specific age to initiate screening, regardless of sexual history. When making their recommendations, the Cervical

Screening Guidelines Development Committee chose not to include a specific age to initiate screening because there is not evidence to support a particular age over another. In addition, linking Pap testing to the initiation of vaginal sexual activity is more practical than choosing a specific age and it is recognized that vaginal transmission of HPV can occur with sexual activities other than intercourse, including vaginal/oral and/or vaginal/digital activity.

The literature regarding the cessation of cervical screening is equally sparse and problematic. Studies have often included women who had never been screened with those that have had adequate screening histories making an evaluation of the evidence difficult. Four of the guidelines recommended that screening should cease between the ages of 65 and 70, however, ACOG reported that there was insufficient evidence to make a recommendation. The study by Colgan et al (33) provided evidence that screening could stop at age 70. They reported that, of the women in their study with HSIL who had negative screening histories, 5% were between 50 and 69 years, and less than 1% were over 70 years. Unfortunately this study did not provide similar information for women with LSIL or any other cervical abnormality.

At What Time Interval Should Women Be Screened?

The evidence regarding the optimal screening interval is also contradictory. The best evidence to date is the retrospective study by Sawaya et al (34) that studied almost a million women who had undergone cervical screening. Their results indicated that screening women every three years, *with conventional cytology or LBC*, was acceptable in terms of the incidence of cervical cancer. However, these results are based on retrospective data, which are susceptible to bias. There has been a move to lengthen the screening interval with the use of LBC. It is argued that the increase in sensitivity can offset the decreased screening frequency and lead to cost reductions associated with the more expensive LBC method. These predictions are largely based on modelling and have yet to be tested. The conclusion of Sawaya et al's study is also based on the assumption that there is an adequate recall mechanism in place to ensure that women are screened every three years. Although a standardized Ontario provincial recall mechanism would be desirable the ability to provide this service is limited by health information privacy legislation. While the Ontario Cervical Screening Program remains committed to developing a recall system, physician offices and medical laboratories also have the potential to develop recall systems. There are many situations in medical practice that require periodic monitoring procedures to be scheduled for patients. The Medicine Act does allow physicians to contact their patients to inform them that health maintenance procedures are due to be carried out (e.g. Pap tests) (64). Thus, the recommended screening interval has been determined based on screening effectiveness, rather than the presence or absence of formal systems to remind patients.

Should Women in Special Circumstances be Screened? (i.e., Women who are Pregnant, Post-Hysterectomy, or HIV Positive, Adolescents, and Women who have Sex with Women,)

The evidence surrounding cervical screening in special populations is limited. There is evidence to indicate that many adolescents are sexually active and at risk for sexually transmitted infections; however, there is no evidence to indicate a different cervical screening regimen. There were no studies identified that targeted cervical screening for pregnant women in terms of optimal screening interval and safety of screening tools. Similarly, no studies were identified to define cervical screening management of women post-hysterectomy, nor were there any studies that targeted the screening of women who are HIV positive in terms of screening interval. There were a number of studies that described cervical screening of HIV-positive women; however, none of them outlined a screening strategy (65-67).

There was evidence to indicate that women who have sex with women should be screened following the same intervals as women who have sex with men. Approximately 80% of women who have sex with women have heterosexual histories (37,38). The incidence of abnormal cytology is similar regardless of sexual orientation; thus, they should follow the same

screening regimen. Only one of the guidelines, the guideline by the NZGG, made a recommendation regarding women who have sex with women (17), indicating that they should be screened similarly to women who have sex with men.

What is the Optimal Management for Women with Abnormal Cytology (up to but not Including Colposcopy/HPV Management)?

There is consensus regarding the management of significant cervical abnormalities including HSIL and referral to colposcopy is a proven practice in cancer prevention. However, the management of low-grade abnormalities including ASCUS and LSIL remains controversial. The introduction of HPV triage for these findings has led to major changes in some jurisdictions while others have recommended against its use or are still assessing the evidence. The 2001 ASCCP guidelines for the management of abnormal cytology were based on evidence and expert opinion (18). Their strongest recommendations were based on the results of the ALTS trial and the utility of HPV testing. The Pan Canadian Forum on Cervical Cancer Prevention provided recommendations on HPV triage for ASCUS but did not refer specifically to LSIL (12). Guidelines in the UK are still being developed pending the results of ongoing study (68). In Australia, the NHMRC did not support the use of HPV testing for managing cervical abnormalities (20).

ASCUS

The ALTS trial has indicated that HPV DNA testing is significantly more sensitive at detecting CIN3 than repeat cytology in women with ASCUS (41,42). The Pan Canadian Forum on Cervical Cancer Prevention recommends HPV triage for women 30 years of age and older with ASCUS (12). The absolute benefit of HPV DNA testing is smaller in younger women than it is among older women because the increased rate of HPV infections and the lower incidence of cervical cancer (58). The absolute probability of benefits of HPV DNA testing among women with ASCUS increase along a continuum with age, whereas the likelihood of harms from HPV DNA testing (unnecessary anxiety, treatment and cost) diminish as age increases. The balance of benefits and potential harms, therefore, grows more favourable as women age. The precise age at which the potential benefits of HPV DNA testing justify the possible harms is a subjective choice. This guideline recommends HPV triage of ASCUS for women aged 30 and older based on current, albeit incomplete evidence. This recommendation will require monitoring of emerging evidence and ongoing impact analysis.

LSIL

In the ALTS trial, the HPV DNA testing arm was terminated early in the group of women with LSIL because of the high percentage of women who were HPV positive (83%) (41). Therefore, colposcopy was determined to be the optimal management for women with LSIL, as HPV DNA testing does not provide sufficient clinical utility to act as a triage test. Furthermore, a summary of the ALTS data indicated that similar rates of CIN 2 or greater were found in women with either LSIL or ASCUS/HPV positive (69). Further review of the ASCCP recommendations was provided by Spitzer et al (70). This article discusses the consideration of age in the management of LSIL. Although no specific evidence or age is defined, the article states, "Even though adolescents have a high incidence of LSIL, they have a very low incidence of developing rapid onset cervical cancer. For selected adolescents, acceptable options for follow-up consist of repeat cervical cytologic analysis at 6 and 12 months with referral to colposcopy when any repeat abnormal cytologic results are ASC or worse, or HPV testing at 12 months with referral to colposcopy for HPV-positive adolescents." A recent publication (71) reviews 260 women aged 13-22 with LSIL followed by cytology and found that 61% regressed by 12 months and 91% regressed by 36 months. This data suggests that colposcopy for young women with LSIL is unnecessary and cytologic follow up is appropriate.

Currently in Ontario, the recommendation for women with LSIL includes both colposcopy and cytologic follow-up. The distribution of referral patterns is currently being studied however, at this time we do not have sufficient information regarding either referral patterns or rates of HPV positivity in the LSIL group. There are concerns that recommending referral of all patients with LSIL to colposcopy will overburden the system. Although HPV triage of this group has potential benefits, especially if the rate of HPV positivity is lower than found in the ATLS trial, there is currently insufficient evidence to recommend its use. Until information on referral patterns and the utility of HPV testing emerge both referral to colposcopy and repeat cytology in 6 months remain acceptable options in Ontario. Repeat cytology should be considered in younger patients and in settings where follow up can be tracked. Again, an Ontario wide system for recall would greatly aid in assuring follow-up and providing necessary data.

Further consideration must be given to the situation of LSIL in a woman with atrophy. Studies have shown that the features of LSIL can be overinterpreted in this setting (72) leading to over-referral to colposcopy. There is limited evidence that intravaginal estrogen use can reverse these changes and clarify the cytologic findings (73). Based on the discussions of the Cervical Screening Guidelines Development Committee, there is consensus that the use of intravaginal estrogen therapy in postmenopausal women reduces atrophy and improves the interpretability of cytology tests. Contraindications to use of estrogen must be considered in this population. In the future, the utility of HPV testing in this group should be determined.

It is obvious that these recommendations will require ongoing review and modification as evidence on cervical cancer screening continues to emerge. This is especially true in the area of HPV testing, both as an adjunct to cytology and as a primary screening tool. It will be vitally important to be able to assess new evidence in the context of the Ontario Health care system. To this end, the completion of a fully integrated database to track screening and management would be invaluable in providing clinical and cost effectiveness information.

ONGOING TRIALS

1. A randomized trial of human papillomavirus testing in primary cervical screening (ARTISTIC). This trial is sponsored and funded by the NHS Research and Development Health Technology Assessment Programme. (<http://www.controlled-trials.com/isrctn/trial/CERVICAL/0/25417821.html>, accessed June 22, 2004)
2. Study of the Feasibility of Implementing Human Papillomavirus Testing in a Family Practice Setting (Ontario). Funded by the Ontario Women's Health Council, and conducted by Cancer Care Ontario and the Ministry of Health and Long-Term Care, the one-year pilot will examine the effectiveness and cost-effectiveness of reflex HPV-DNA testing as a follow-up test for women with specific abnormalities on their Pap tests in the family practice setting. The pilot will also examine current evidence and feasibility of HPV self-testing as an alternative for women who cannot regularly have a Pap test due to geographic location. Further, information needs of physicians and patients will be reviewed. Proposed completion date for this study is the end of 2005.
3. TOMBOLA (trial of management of mild and borderline cervical abnormalities) study. TOMBOLA is a randomized controlled trial to determine the most effective and efficient management strategy for women with borderline or mildly dyskaryotic cervical smear results, and the most appropriate treatment for women with abnormalities detected following colposcopy. The seven-year multi-centre trial (Dundee, Aberdeen and Nottingham) started recruitment of women in December 1999 and aims to recruit 10,000 women.

CONFLICT OF INTEREST

The members of the Gynecology Cancer DSG disclosed potential conflicts of interest relating to the topic of this practice guideline. One collaborator is employed by MDS Diagnostic Services and

has investments with MDS. Another collaborator is a consultant for MDS Diagnostic Services and receives honoraria from MDS for his contributions. Four collaborators are currently involved in a trial examining the results of the implementation of SurePath in Ontario, and four collaborators are involved in a trial investigating the feasibility of implementing HPV testing in a family practice setting. Two collaborators are members of the Cytobase Data Review Committee, and another collaborator is the chair of cytology at QMP-LS. No other conflicts of interest were declared.

JOURNAL REFERENCE

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For a complete list of the Gynecology Cancer DSG members and the Practice Guidelines Coordinating Committee group members, please visit the CCO Web site at <http://www.cancercare.on.ca/>

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Evidence-based Series: Section 3

Cervical Screening: Guideline Development and External Review: Methods and Results

C.M. McLachlin, V. Mai, J. Murphy, M. Fung Kee Fung, A. Chambers, and members of the Cervical Screening Guidelines Development Committee of the Ontario Cervical Screening Program and the Gynecology Cancer Disease Site Group of Cancer Care Ontario.

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)
Developed by the Gynecology Cancer Disease Site Group

Report Date: May 20, 2005

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The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

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The Evidence-based Series: A New Look to the PEBC Practice Guidelines

Each Evidence-based Series is comprised of three sections.

- *Section 1: Clinical Practice Guideline.* This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review by Ontario practitioners.
- *Section 2: Systematic Review.* This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.

- *Section 3: Guideline Development and External Review: Methods and Results.* This section summarizes the guideline development process and the results of the formal external review by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This evidence-based series was developed by the Gynecology Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care (PEBC). The series is a convenient and up-to-date source of the best available evidence on cervical screening, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

Disease Site Group and Collaborating Group Consensus

The Cervical Screening Guidelines Development Committee met to discuss the draft guideline. The group went through the sections of guideline individually and discussed how the evidence supported the recommendations. There was general consensus regarding the recommendation to indicate that LBC was the preferred screening tool over conventional cytology.

In terms of the initiation of cervical screening, the group extensively discussed the optimal wording of the recommendation. The group chose not to include a specific age to initiate screening because there are women who are not sexually active by 18 or 21 (recommended ages in other guidelines), and did not want to recommend that these women be screened.

For the cessation of screening, the group spent some time discussing the potential high-risk sexual behaviours of older women. Ultimately the group decided not to make recommendations based high risk behaviours in older women because the group felt it would complicate the recommendations, also there was no evidence identified to support different screening regimens for high risk older women.

There was some discussion regarding the optimal screening interval especially regarding necessary recall mechanisms for a three-year screening interval. The need for recall mechanisms either within the primary care practice or as part of the provincial registry was emphasized before a three-year interval should be considered.

Unfortunately, there is little evidence regarding cervical screening for women in special circumstances. For this reason, the group decided that it was important to clearly state throughout the guideline where there was evidence and where expert opinion was utilized.

For the recommendations regarding abnormal cytology, the group discussed simply endorsing the ASCCP guidelines because of similarities to the Ontario setting. However, after some debate the group agreed that there are important differences in recommendations in the guideline compared to the ASCCP guidelines (Table 1). It was important to the group to make the guidelines specific to the population of women in Ontario.

Table 1. Differences between the ASCCP recommendations and the recommendations of this Ontario practice guideline.

Abnormal cytology	ASCCP (18)		Ontario guideline	
	Recommendation	Evidence	Recommendation	Evidence
ASCUS	<ul style="list-style-type: none"> • HPV DNA testing preferred • Repeat cytology (4-6 months) • Colposcopy (no conditions when it is appropriate given) 	<ul style="list-style-type: none"> • ALTS trial—HPV DNA testing is more sensitive than cytology or colposcopy 	<ul style="list-style-type: none"> • HPV DNA testing preferred for women >=30 yrs • Repeat cytology (6 months) • Colposcopy—if there is a high probability of patient loss to follow up, or if there are other symptoms suggesting cervical abnormality 	<ul style="list-style-type: none"> • ALTS trial—HPV DNA testing is more sensitive than cytology or colposcopy
Postmenopausal women with ASCUS	<ul style="list-style-type: none"> • Intravaginal estrogen therapy + repeat cytology • Colposcopy or HPV DNA testing 	<ul style="list-style-type: none"> • Expert opinion/ consensus 	<ul style="list-style-type: none"> • No evidence to make recommendation 	
LSIL	<ul style="list-style-type: none"> • Colposcopy 	<ul style="list-style-type: none"> • ALTS trial—colposcopy because colposcopy detected most cases on CIN3 on first visit 	<ul style="list-style-type: none"> • Colposcopy or repeat cytology 	<ul style="list-style-type: none"> • ALTS trial—colposcopy because colposcopy detected most cases on CIN3 on first visit • Expert opinion/consensus
Young women with LSIL	<ul style="list-style-type: none"> • Repeat cytology • HPV DNA testing • Colposcopy 	<ul style="list-style-type: none"> • Age of young women not defined • HPV DNA arm stopped early in ALTS trial because too many women were found to be HPV positive • Expert opinion/ consensus 	<ul style="list-style-type: none"> • No evidence to indicate that young women should be managed differently from other women. However, expert opinion suggests considering cytology follow up in younger women 	
Postmenopausal women with LSIL	<ul style="list-style-type: none"> • Intravaginal estrogen therapy + repeat cytology • Colposcopy or HPV DNA testing 	<ul style="list-style-type: none"> • HPV DNA arm stopped early in ALTS trial because too many women were found to be HPV positive • Expert opinion/ consensus 	<ul style="list-style-type: none"> • Limited evidence suggests utility for intra-vaginal estrogen use prior to repeat cytology 	
ASC-H, AGC, HSIL	<ul style="list-style-type: none"> • Colposcopy 	<ul style="list-style-type: none"> • ALTS trial data • Retrospective data 	<ul style="list-style-type: none"> • Colposcopy 	<ul style="list-style-type: none"> • ALTS trial data • Retrospective data

External Review by Ontario Clinicians

Following review and discussion of sections 1 and 2 of this evidence-based series, the Gynecology Cancer DSG circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Box 1 summarizes the draft clinical recommendations and supporting evidence developed by the panel. Please note that recommendation evidence ratings are in brackets, the scale for which can be found in Appendix 1 of Section 1.

<p>BOX 1: DRAFT RECOMMENDATIONS (approved for external review September 15, 2004)</p>
<p><i>Target Population</i> All women who are, or have ever been, sexually active, not including women with special circumstances, or women with abnormal cytology</p>
<p><i>Recommendations</i> <u>Optimal cervical screening tool</u></p> <ul style="list-style-type: none"> • Liquid-based cytology (LBC) is the preferred tool for cervical cytology screening (B-II). Conventional smear cytology remains an acceptable alternative (C-III). <p><u>Optimal screening circumstances</u></p> <ul style="list-style-type: none"> • Given the lower incidence and mortality of organized screening programs elsewhere, a province-wide cervical screening program with an adequate recall mechanism is recommended (A-II). <p><u>Screening initiation</u></p> <ul style="list-style-type: none"> • Cervical cytology screening should be initiated within three years of first vaginal sexual activity (i.e. vaginal intercourse, vaginal/oral and/or vaginal/digital sexual activity) (C-III). <p><u>Screening Interval</u></p> <ul style="list-style-type: none"> • Screening should be done annually until there are three consecutive negative Pap tests (C-III). • Screening should continue every two to three years after three annual negative Pap tests (B-II). <ul style="list-style-type: none"> ○ Screening at a three-year interval is recommended, supported by an adequate recall mechanism (B-II). ○ Women who have not been screened in more than five years should be screened annually until there are three consecutive negative Pap tests (C-III). <p><u>Screening Cessation</u></p> <ul style="list-style-type: none"> • Screening may be discontinued after the age of 70 if there is an adequate negative screening history in the previous 10 years (i.e. 3-4 negative tests) (B-II).
<p><i>Target Population</i> Women with special circumstances (i.e. women who are pregnant, post-hysterectomy, postmenopausal, HIV positive, adolescents, and women who have sex with women).</p>
<p><i>Recommendations</i></p> <ul style="list-style-type: none"> • Immunocompromised or HIV positive women should receive annual screening (C-III). <ul style="list-style-type: none"> ○ Examples of situations where women may be immunocompromised include women who have received transplants and women who have undergone chemotherapy. • Screening can be discontinued in women who have undergone total hysterectomy for benign causes with no history of cervical dysplasia or human papillomavirus (C-III). <ul style="list-style-type: none"> ○ 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 women who are not pregnant (B-III). Manufacturer's recommendations for the use of individual screening tools in pregnancy should be taken into consideration. • Women who have sex with women should follow the same cervical screening regimen as women who have sex with men (B-II).
<p><i>Target Population</i> Women with abnormal cytology (i.e. ASCUS, ASC-H, LSIL, HSIL, and AGC).</p>
<p><i>Recommendations</i></p> <ul style="list-style-type: none"> • Women with ASCUS (Atypical squamous cells of uncertain significance) <ul style="list-style-type: none"> ○ HPV DNA testing with cytology is recommended for women aged 30 or older with ASCUS (C-III). <ul style="list-style-type: none"> ▪ 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).

<ul style="list-style-type: none"> <ul style="list-style-type: none"> <ul style="list-style-type: none"> ▪ 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 (abnormal bleeding, etc.) (A-I). • Women with ASC-H (Atypical squamous cells: cannot exclude high grade squamous) <ul style="list-style-type: none"> ○ Colposcopy is recommended for women with ASC-H (A-II). • Women with LSIL (Low-grade squamous intraepithelial lesion) <ul style="list-style-type: none"> ○ Either colposcopy or repeat cytology in six months is recommended for women with LSIL (B-II). <ul style="list-style-type: none"> ▪ 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). • Women with HSIL (High-grade squamous intraepithelial lesion) <ul style="list-style-type: none"> ○ Colposcopy is recommended for women with HSIL (A-II). • Women with AGC (Atypical glandular cells) <ul style="list-style-type: none"> ○ Colposcopy is recommended for women with AGC (A-II). ○ Women with AGC should also receive endocervical and endometrial sampling, where appropriate (A-II).
<p><i>Qualifying Statements</i></p> <ul style="list-style-type: none"> • 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.

Practitioner Feedback

Based on the evidence and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods

Practitioner feedback was obtained through a mailed survey of 180 physicians (129 family practitioners and pathologists [from supplied lists] and 51 practitioners from the PEBC database [30 medical oncologists, one radiation oncologist, 11 surgeons, and nine gynecologists]) across the province on September 15, 2004. Reminder postcards went out to the non-responders on September 29, 2004 and a second reminder (full package) was sent out on October 13, 2004. A third mailing (full package) went out on November 9, 2004.

Results

As of January 17, 2005, 35 of the 129 questionnaires sent out to family practitioners and pathologists had been returned (27% return rate). Of the 35 returns, all 35 respondents (100%) indicated that the draft practice guideline report was relevant to their clinical practice and completed the survey.

Of the questionnaires sent to practitioners from the PEBC database, 20 questionnaires were returned (39% return rate). Of the 20 returns, five respondents (25%) indicated that the draft practice guideline report was relevant to their clinical practice and completed the survey. Key results of the practitioner feedback survey are summarized in Table 2.

Table 2. Practitioner responses to items on the practitioner feedback survey.

Item	Number (%)			Number
	Strongly agree or agree	Neither agree nor disagree	Strongly disagree or disagree	No answer
The rationale for developing a clinical practice guideline, as stated in the "Choice of Topic" section of the report, is clear.	34 (97%) <i>5 (100%)</i>	1 (3%) -	- -	- -
There is a need for a clinical practice guideline on this topic.	34 (97%) <i>5 (100%)</i>	1 (3%) -	- -	- -
The literature search is relevant and complete	26 (74%) <i>4 (80%)</i>	7 (20.0%) <i>1 (20%)</i>	2 (6%) -	- -
The results of the trials described in the report are interpreted according to my understanding of the data.	32 (91%) <i>4 (100%)</i>	2 (6%) -	1 (3%) -	- <i>1</i>
The draft recommendations in this report are clear.	35 (100%) <i>5 (100%)</i>	- -	- -	- -
I agree with the draft recommendations as stated.	32 (91%) <i>4 (80%)</i>	1 (3%) -	2 (6%) <i>1 (20%)</i>	- -
The DRs reflect a more effective approach for improving patient outcomes than is current usual practice (if DRs are the same as current practice, please tick NA†).*	17 (50%) <i>3 (60%)</i>	6 (17.7%) <i>1 (20%)</i>	3 (8.8%) <i>1 (20%)</i>	n/a = 8 (23.5%) <i>1</i> -
When applied, the DRs will result in better use of resources than current usual practice (if DRs result in the same outcomes as current practice, please tick NA†).*	23 (67.8%) <i>1 (20%)</i>	3 (8.8%) <i>2 (40%)</i>	2 (5.8%) <i>2 (40%)</i>	n/a = 6 (18%) <i>1</i> -
This PGIP report should be approved as a practice guideline.	32 (94%) <i>4 (80%)</i>	- -	2 (6%) <i>1 (20%)</i>	1 -
If this PGIP report were to become a practice guideline, how likely would you be to make use of it in your own practice?	Likely or very likely	Unsure	Not at all likely or unlikely	No answer
	30 (86%) <i>4 (80%)</i>	2 (6%) -	3 (9%) <i>1 (20%)</i>	- -

NOTE: The numbers in bold reflect the 28 responses from family practitioners and pathologists. The numbers in italics reflect the corresponding figures from practitioners in the PEBC database. Some items do not total 100% due to rounding.

Summary of Written Comments

Two of the five respondents from the PEBC database provided written comments. The main points in the written comments were:

1. Questionable impact on outcome because strategies to attract and retain patients were not addressed, and therefore recommended information on this issue be addressed
2. Disagreement with the three-year screening interval stating that HPV typing of ASCUS smears by family physicians prior to referral would be expensive and impractical.

Eighteen of the 35 family practitioner and pathologist respondents (51%) provided written comments. Three main areas within the guideline were a concern for a number of the respondents. Those concerns are as follows:

3. Liquid-based cytology (LBC):

- Concern arose around the difficulty in implementing cervical cytology screening as the preferred method due to the public sector using PAP smears and the private using LBC.
- The guideline ought to report LBC as the preferred, not only, method and consider the false negative rates due to sampling for the LBC samples.
- LBC should be rated as B-11 not A-11.

4. Testing coverage:

- Implementation of the guideline rests on HPV testing being covered by OHIP.

- HPV testing at patient cost would be too difficult to implement.
 - Since patients may request PAP tests more often than the guideline specifies, there should be a guideline option for patients to pay for PAPs if they request more than the guideline specifies.
5. Three-year screening intervals:
 - The extended length of time between screening may result in delayed STD testing and counselling.
 - The length of time may be unsafe because technology may not be sensitive enough to catch disease every time.
 - Patients may be unable to remember PAP results, thereby making it difficult to determine who requires a PAP every 3 years.
 - More information needs to be provided that describes an “adequate recall mechanism.”
 6. More detailed information needs to be provided for those unfamiliar with epidemiological terminology.
 7. The guideline needs to respond directly to other guidelines that use age only initiation criteria
 8. The guideline needs a recommendation on pregnancy sampling methods.
 9. A statement needs to be added regarding pelvic exam intervals in the absence of PAP smears
 10. The guideline needs to be flexible to accommodate all patients and a guideline applied too rigidly may cause harm to patients.
 11. The central registry is a key element missing from the guideline.
 12. All LSIL referrals to colposcopy are impractical.

Overall, seven respondents (33%) made positive remarks about the guideline and commented on the need for it in the health care system.

Modifications/Actions

In response to practitioner feedback, the practice guideline was changed in the following ways:

1. Recruitment and recall is the main activity of one of the committees of the Ontario Cervical Screening Program
2. It was acknowledged that funding of HPV testing within the provincial system would be necessary for ASCUS triage to be implemented. Discussions with the MOHLTC are ongoing.
3. Implementation issues around LBC were acknowledged as well as the funding issue for hospitals versus community based laboratories. The authors agreed that LBC should be the preferred but that conventional cytology remains acceptable and changed the recommendation accordingly. The LBC rating was changed from A-11 to B-11.
4. See 2.
5. The screening interval of two to three years allows for some individualization depending on available recall mechanisms, etc. Recall mechanisms are further discussed in the interpretive summary. The screening interval should not affect annual health exams.
6. Further explanations have been added.
7. Further information was added to the interpretive summary.
8. The use of proprietary sampling devices is covered by manufacturer’s specifications.
9. The need for continued health exams will be stressed.
10. Individual use of guidelines should allow for modifications depending on the full patient history.
11. The need for a central registry along with a recall system has been stressed in the interpretive summary.
12. The issue of optimal management of LSIL was extensively reviewed and the recommendations revised to include the option of repeat cytology in 6 months.

Practice Guidelines Coordinating Committee Approval Process

The practice guideline report on cervical screening was circulated to 13 members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Five members of the PGCC approved the report as written. Three members approved the report as written, but requested that minor modifications be made. One PGCC member approved the report conditional on specific changes being made and requested a response from the guidelines development group.

Summary of Written Comments

1. One member asked that the key evidence be grouped with the guideline recommendations when there were multiple guideline questions being addressed.
2. One member also asked that a fuller description of screening technique for conventional and LBC screening.
3. One member commented that the recommendations do not really answer the second question regarding the benefit of a recall system.
4. One member asked that “vaginal activity” be explicitly defined in regard to the recommendation concerning initiation of screening.
5. One member found that recommendation around screening initiation, interval, and cessation was confusing and suggested that the section be re-written to improve clarity.
6. One member questioned the evidence concerning whether older women, who haven’t been screened in more than five years, should still be screened annually until there are three consecutive negative Pap tests.

Modifications/Actions

1. While there is merit in presenting the key evidence after each recommendation, the authors felt that this approach would hamper the presentation of the recommendations as a whole, and notes that an evidence rating system was used for each recommendation.
2. In section II-b on Page 2 a brief description of the sampling and preparatory techniques for conventional and liquid based cytology is present. The following sentence confirming the similar screening method used for both preps was added: "Both conventional and LBC samples are screened by cytotechnologists in a similar fashion".
3. The evidence for the benefit of a recall system is listed in Section IV-2, specifically regarding the success of the UK system. The recommendation was revised to read: "Given the lower incidence and mortality of organized screening programs elsewhere, a province-wide cervical screening program with an adequate recall mechanism is recommended (A-II)".
4. The wording “vaginal sexual activity” was specially chosen to exclude other types of sexual activity that would not put a woman at risk for contracting a cervical HPV infection. As well “sexual activity” was chosen to include intercourse, oral and digital transmission. The recommendation was revised to read: "Cervical cytology screening should be initiated within three years of first vaginal sexual activity (i.e. vaginal intercourse, vaginal/oral and/or vaginal/digital sexual activity) (C-III)".
5. This guideline includes recommendations for the follow up of abnormal Pap tests up to but not including colposcopic management. A new committee is currently being organized to develop guidelines for colposcopic management and follow up. Therefore for women that have a single abnormal cytology (ASCUS or LSIL), not requiring colposcopy, this guideline does contain recommendations for when these women can return to regular screening. The upcoming colposcopic guidelines should include similar recommendations for women that have undergone colposcopic evaluation. The section was revised to improve clarity as follows: "There is evidence presented that negative pap testing can provide a significant protection from cervical cancer for up to five years. It is also known that women after the age of 30 often have only sporadic pap smears".
6. This recommendation was included to assure optimal screening in older women who are most at risk of cervical cancer.

REFERENCES

1. Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol.* 1995;13:502-12.
2. Browman GP, Newman TE, Mohide EA, Graham ID, Levine MN, Pritchard KI, et al. Progress of clinical oncology guidelines development using the practice guidelines development cycle: the role of practitioner feedback. *J Clin Oncol.* 1998;16(3):1226-31.