



LIQUID-BASED TECHNIQUES AND HUMAN PAPILLOMAVIRUS TESTING: NEW OPTIONS FOR CERVICAL CANCER SCREENING

RESEARCH HIGHLIGHTS - FEBRUARY 2008

This document highlights key findings from a CADTH health technology assessment report on the clinical and cost-effectiveness of liquid-based techniques for cervical cancer screening.

Following the introduction of the Papanicolaou (Pap) smear in the 1950's, the incidence of cervical cancer in Canada declined significantly. In 2007, it's estimated that 1,350 women will be diagnosed with cervical cancer in Canada, and 390 will die as a result of the disease.

Until recently, the only option for cervical cancer screening was conventional cytology with an annual Pap smear. However, two new technologies – liquid-based cytology and testing for the presence of human papillomavirus, a virus responsible for almost all cases of cervical cancer – offer options for new screening strategies.

But...what is the role of the newer technologies? Will they optimize health compared to CC? What approach to cervical cancer screening in Canada constitutes the most rational use of resources?

CONVENTIONAL CYTOLOGY (CC)

- A sample of cells are taken from the cervix using a spatula or brush.
- The cells are smeared onto a glass slide or plate.
- The cells are immediately “fixed” using a spray fixative.
- The slide is sent to the laboratory for examination.

KEY FINDINGS

- LBC and CC perform similarly
- LBC strategies can be cost-effective, but increase colposcopy referrals
- HPV triage is cost-effective

LIQUID-BASED CYTOLOGY (LBC)

- A sample of cells from the cervix is collected in a similar manner to CC.
- The sample is immediately placed in a liquid fixative medium.
- The sample is sent to the laboratory where a slide is prepared.
- Two preparation systems currently approved in Canada:
 - ThinPrep Pap Test (Cytoc Corporation)
 - SurePath Pap Test (BD Diagnostics/TriPath Imaging Inc.).
- Both systems require proprietary sampling tools, fixatives, and preparation devices.

HUMAN PAPILLOMAVIRUS (HPV) TESTING

- Detects HPV DNA within cervical cells.
- Types of HPV DNA tests include:
 - AMPLICOR
 - Hybrid Capture 2
 - Other techniques being developed.



- Some laboratories use polymerase chain reaction (PCR) methods for detecting HPV DNA, but these lack standardization and are labour- intensive.
- Linear Array HPV genotyping tests are also available.

FOR HEALTH CARE PROVIDERS

Why LBC?

- The goal of LBC is to enhance the detection of pre-cancerous lesions through **improved sample and cell preparation**.
- LBC also **allows for HPV DNA testing on the same sample**, enabling a triage of ASCUS results – abnormal results of undetermined significance.

Why HPV Triage?

- With CC, following **ASCUS**, repeat cytology is often the course of action.
- With HPV DNA testing an ASCUS result can be “triaged” based on whether or not a high-risk (oncogenic) type of HPV DNA is present.
 - Those with a high-risk HPV infection are sent for immediate colposcopy.
 - Those without a high-risk HPV infection can avoid colposcopy and continue to be screened at regular intervals.

Clinical Effectiveness Results

Based on data from 20 studies (68,114 participants):

- LBC is, on average, 6% more sensitive and 4% less specific than CC:
 - Mean sensitivity of LBC=81%; of CC=74%
 - Mean specificity of LBC=83%; of CC=87%.
- LBC, on average, had slightly fewer unsatisfactory samples.
- Frequent screening with LBC in place of CC in current programs, without increased screening intervals, increases colposcopy rates.
- HPV triage of ASCUS offers increased sensitivity and similar specificity to repeat cytology.

FOR POLICY MAKERS, ADMINISTRATORS, AND SCREENING PROGRAM MANAGERS

With Current Screening Programs:

- 46 women need to be screened during a lifetime to avoid one cervical cancer case.
- 109 (estimated) would need to be screened to prevent one death.

Extending current screening programs to two-year screening intervals would:

- increase cervical cancer incidence and mortality by approximately 7%.

Comparing Liquid-based Cytology versus Conventional Cytology (Pap testing)

Sampling Technology	Pros	Cons
CC (Pap)	<ul style="list-style-type: none"> • Simple • Inexpensive • Most commonly employed technique (i.e., established) 	<ul style="list-style-type: none"> • Significant false-negative rates occur due to sampling, preparation, screening, and interpretation errors • Does not allow for HPV testing on the same sample
LBC	<ul style="list-style-type: none"> • Provides a uniformly fixed and distributed sample of cells • Allows for HPV testing on the same sample 	<ul style="list-style-type: none"> • Both preparation systems require proprietary sampling tools, fixatives, and preparation devices, and represent additional investment and infrastructure change.



Screening Options Compared to Current Screening Programs

Screening Option	CC plus HPV Triage 2-year Interval	Liquid-based Cytology (LBC) 2-year Interval	LBC plus HPV Triage 2-year Interval
Relative Incidence of Cancer	<ul style="list-style-type: none"> Increase by 2% 	<ul style="list-style-type: none"> Unchanged 	<ul style="list-style-type: none"> Decrease by 6% The only screening option to reduce disease incidence at 2-year screening interval
Colposcopy Referrals	<ul style="list-style-type: none"> Decrease by 19% 	<ul style="list-style-type: none"> Increase by 48% 	<ul style="list-style-type: none"> Increase by 37.5%
Lifetime Costs	<ul style="list-style-type: none"> Lower average lifetime costs (\$77 per person, discounted) 	<ul style="list-style-type: none"> Lower average lifetime costs (\$39 per person, discounted) 	<ul style="list-style-type: none"> Lower average lifetime costs (\$59 per person, discounted)

With Liquid-based Cytology:

- For screening intervals ≥ 3 years, LBC was economically attractive [range: \$1,000 to \$52,000 per life-year (LY) gained].
- For shorter screening intervals, LBC was less attractive:
 - Two-year screening interval: \$5,000 to \$132,000; median \$41,000 per LY gained
 - One-year screening interval: \$21,000 to \$516,000; median \$186,000 per LY gained.

With HPV Triage:

HPV triage was more effective for ASCUS than repeat cytology, resulting in:

- reduced disease incidence
- reduced colposcopy referrals
- extended life-years.

For screening intervals ≥ 3 years, HPV triage strategies appeared to be somewhat attractive (\$300 to \$61,000 per LY gained), but results were inconsistent for shorter intervals.

Direct comparisons show that annual screening with CC or LBC is always more costly and less effective than when paired with HPV triage.

Model projections suggest that during a woman's lifetime:

- LBC is likely to reduce cervical cancer (and related) mortality at increased costs compared with CC, at the same screening interval.

- HPV triage reduces costs and improves health outcomes (when paired with either LBC or CC).

An LBC-based HPV triage program would cost an additional \$6.35 per targeted individual.

The Health Economic evidence suggests that HPV triage, together with CC or LBC annually or every two years, is a better use of health care resources than current screening strategies. The best use of resources for cervical cancer screening are observed with:

- LBC and HPV triage annually
- LBC and HPV triage every two years
- CC and HPV triage annually.

GLOSSARY OF IMPORTANT TERMS

ASCUS (Atypical Squamous Cells of Undetermined Significance) – a Pap smear result that is slightly abnormal for unknown reasons and may or may not be cause for concern.

Cervical Cancer – cancer of the lower part of the womb or uterus. The cervix is sometimes called the “neck” of the uterus.



Colposcopy – a medical procedure in which a health care professional uses a lighted magnifying tool (called a colposcope) to examine the vagina and cervix.

Cytology – the medical and scientific study of cells allowing the diagnosis of disease.

Human papillomavirus (HPV) – a family of viruses that are transmitted by skin-to-skin contact. Some types of HPV cause warts and others are associated with different types of genital cancers, including cancer of the cervix.

LBC (Liquid-based Cytology) – a newer alternative to conventional cytology (Pap smears) for cervical cancer screening.

QALY (Quality-Adjusted Life-Year) – an extra year of healthy life expectancy.

Papanicolaou (Pap) Test/Smear – a screening test for cervical cancer where cells from the cervix are examined under a microscope. The cells are collected from the cervix during a pelvic exam.

Screening Interval – the length of time between two screening tests (i.e., the number of years between Pap tests).

Sensitivity – how well a test works in identifying people with a certain condition.

Specificity – how well a test works in detecting only those people with a certain condition (and not those without the condition).

Willingness To Pay (WTP) – how much a decision maker is willing to pay for an extra year of healthy life expectancy (QALY).

The results of this report will require revision with the introduction of automated screening, HPV vaccinations, and organized screening programs.

PROJECT INFORMATION

With the recent availability of alternative technologies for cervical cancer screening, such as liquid-based cytology, as well as the introduction of HPV DNA testing, the ideal approach to screening in Canada has been in question. LBC for cervical cancer screening remains controversial, with some provinces having adopted the technology and others still considering it. CADTH initiated a systematic review and cost-effectiveness analysis of liquid-based techniques for cervical cancer screening in May 2006 to provide evidence to help answer this question.

The research lead for the project was Dr. Murray Krahn from the University of Toronto. The primary report author was a BPharm, PhD candidate from the University of Toronto.

CADTH's full-length LBC report, *Liquid-Based Techniques for Cervical Cancer Screening: Systematic Review and Cost-Effectiveness Analysis*, as well as a Technology Overview and this Research Highlights tool, are available at www.cadth.ca.

ABOUT CADTH

The Canadian Agency for Drugs and Technologies in Health (CADTH) is a national body that provides Canada's federal, provincial and territorial health care decision makers with credible, impartial advice and evidence-based information about the effectiveness and efficiency of drugs and other health technologies.

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