



Pap Smears: A review of what's new

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Is there a problem?

The Pap smear has been touted as the greatest screening test ever discovered. Indeed, Dr. Papanicolaou, the father of the Pap smear, had a United States stamp created in his honor in 1980.¹ Since that time, however, the value and utility of the Pap smear has come into question. The concern about false-negative Pap smears, missed cancers, litigation and newer technology necessitates a review of cervical cancer screens.

Review of events

The Pap smear was discovered serendipitously by Dr. Papanicolaou during hormonal evaluation of vaginal smears in guinea pigs and humans in the 1920s. Cancer cells were seen in the vaginal sample of a hospital volunteer. These findings were first published in 1941, but it was not until 1949 that the Pap test was used for screening.² Over the following decades, the Pap smear was adopted for widespread use in several regions and provinces in Canada, the United States and Europe, resulting in a 90% reduction of invasive cervical cancer.

In developing countries, where there is no access to Pap smear screening, cervical cancer affects up to

5% of all women. This figure is just under half the one in nine women who will get breast cancer in those countries. In nations where Pap smear screening is available, approximately 1% of women will be affected by cervical cancer. Currently 2.5 women per 100,000 die in North America due to this disease. A target of 1.3 deaths per 100,000 women is recommended — in Canada there were an estimated 1,450 new cases and 420 deaths in 2001.

In 1976, the Walton report was prepared in response to a task force reviewing cervical cancer in Canada.³ The necessity for an organized cervical cancer screening program was outlined and recommendations made for the creation of central registries for recruitment and recall of women.

The issue of organized screening was revisited by national task forces in Canada in 1982, 1989 and more recently in 1995, to determine if the 1989 recommendations were still applicable.³ Since 1976, few countries have invested in organized screening programs (Table 1). The reasons described for this void include “lack of political will, lack of understanding by decision-makers to long-term investment” and management by stakeholders who benefit from annual screening.¹

Pap smear

Table 1

Components of an Organized Screening Program

- = Participant recruitment.
- = Information systems for registration and recall.
- = Quality control review and improvement.
- = Education for service providers and attendees.

Screening

Before reviewing the issues behind the perceived failures of Pap smear screening, it is important to review the basic concepts of a screening test. To recall, a screening test is not a diagnostic test. Screening refers to early detection of a disease process where members of the general public are separated into those with higher and lower probabilities of disease. The former group should then undergo diagnostic tests and, if diseased, receive treatment.

Conditions for screening include: a target disease that is an important cause of mortality and morbidity; a proven and acceptable test (tolerable to patients and cost-efficient) to detect individuals at an early stage of the disease; available treatment to prevent mortality and morbidity once positives have been identified; and a latent period in the natural history

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Table 2

Steps for Cervical Screening

- = Participant attendance.
- = Performing a satisfactory smear of the transformation zone.
- = Fixation and staining.
- = Identification of abnormal areas.
- = Classification of abnormality.
- = Recommendation for investigation and treatment.
- = Attendance of investigation and treatment.
- = Completed treatment.
- = Further followup within the system.

to allow for detection and treatment. Sensitivity and specificity of the test are important parameters in evaluating the test's utility, as are the predictive values of the test (Table 2).

It is critical to understand that screening cannot be 100% effective and has its expected limitations. A pap smear slide review by a cytotechnologist has modest test performance characteristics. When cytology is compared with a reference of biopsy and colposcopy for a minimum of cervical intraepithelial neoplasia, grade 1 (CIN1) — mild dysplasia — or greater, sensitivity ranges from 30% to 87% (average 47%) and specificity from 86% to 100% (aver-

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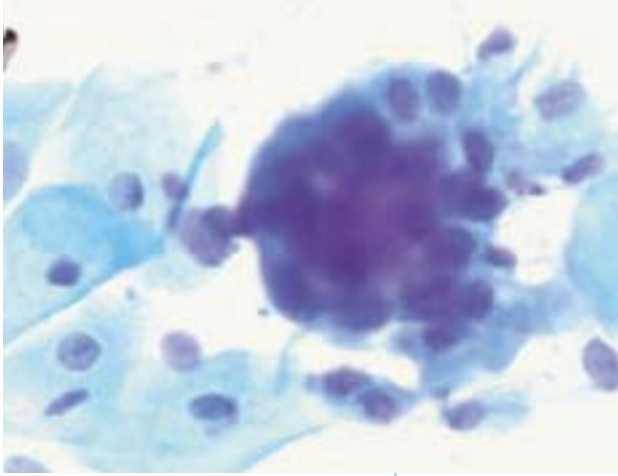


Figure 1: HSIL with drying artifact that looks like normal dried endocervical cells. Note normal endocervical cell under arrow.

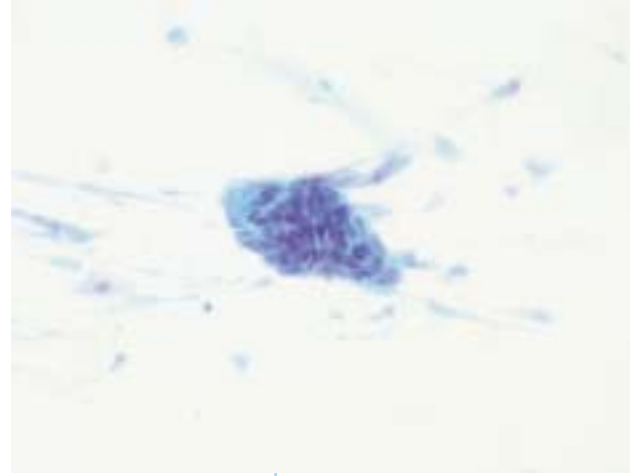


Figure 2: HSIL with drying artifact that looks like normal endocervical cells.

age 95%). Detection of invasive cancer is not the purpose of the Pap smear and, thus, the poor sensitivity due to inflammation, blood and necrosis in the presence of a gross tumor is understandable.

The Pap smear used to detect precursor lesions of cervical cancer fulfills all the criteria of a screening test. Used in an “organized” screening program, it is cost-effective, with maximal ability to decrease mortality and morbidity of invasive cervical cancer. The smears from an organized program have the greatest impact, while opportunistic smears outside the program have less impact as they are too often taken from younger women of child-bearing years. Proponents of organized screening criticize the wasteful inefficient tendency of practitioners to perform frequent opportunistic smears despite the “cost-ineffectiveness” of this approach.⁶ Where organized screening does not exist, this is the best that can be done and has nonetheless decreased the incidence and mortality of invasive cervical cancer by 90%. This rate can be better.

Despite an apparent consensus that organized screening is the most cost-effective and optimal way to deliver cervical cancer screening, in over a quarter of a century this has not been achieved in Canada, North America and most of Europe. As a result,

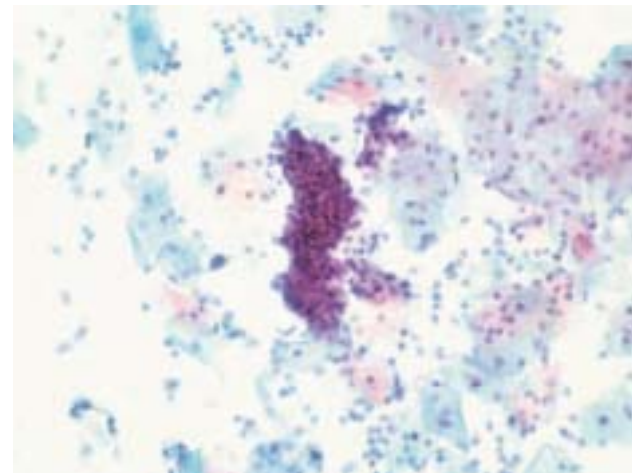


Figure 3: A group of endocervical appearing cells that are actually adenocarcinoma in situ.

women are still being diagnosed with, not only invasive cervical cancer, but advanced stages of the disease that are incurable. Of these women, 50% have never had a Pap smear, 10% have not had one within five years of diagnosis, 10% had inappropriate triage and followup, and 30% of cases were due to sampling or interpretation errors of the Pap smear. Clearly, 60% of the incidence of, and mortality from, cervical cancer could be alleviated by recruiting patients for an organized screening program.

Pap smear

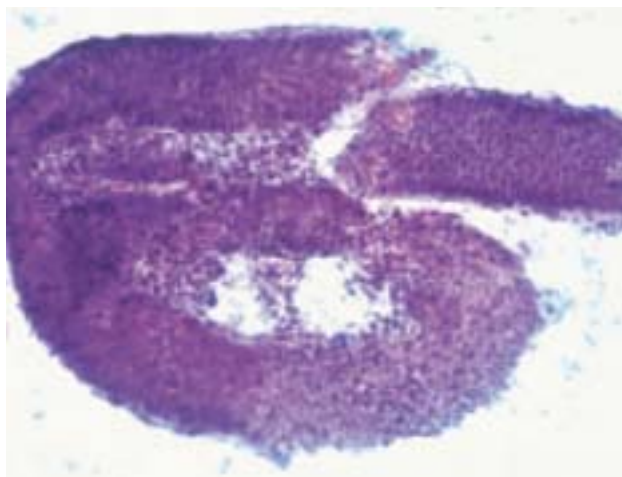


Figure 4: Proliferative endometrial cells caused by cyto-brush removal. Note the similarity to Figure 5, which is a case of endometrial cancer.

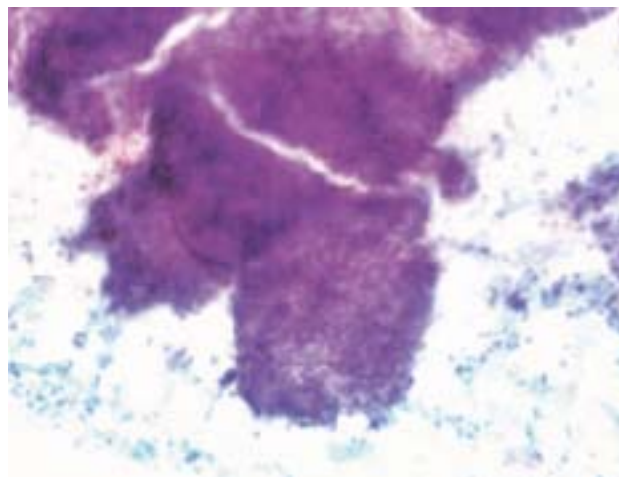


Figure 5: Endometrial cancer accidentally picked up on Pap smear.

Table 3

New Developments for Cervical Screening

Device/Test	Benefits	Concerns	Availability
HPV testing	Detect 13 high risk	Cost	Commercial
Hybrid Capture 2	HPV subtypes	Overtreatment Specificity	Recommended in clinical studies ASCUS
Computerized review			
PAPNET	Identify abnormal cells, project images	Cost Human review	Commercial
AutoPap 300QC	Algorithms to identify abnormal slides for further review. 3 levels, 10%, 15% , 20%	Cost Human review	Commercial but no longer available
AutoCyte (screen)	Presents images for human and computer decisions regarding abnormality.	Cost Human review	Commercial
Human pappillomavirus vaccine (HPV)	Prevent HPV infection	Immune reaction	Experimental

The Crisis

Over the past two decades, the Pap smear has come under attack by the media and challenged, creating a climate of uncertainty and distrust. Abuses and avoidable errors in screening have been brought to the forefront and have exacerbated the known limitations of a screening test.

Since the publication of two *Wall Street Journal* articles by Walt Bogdanich in 1987, outlining failures in the system (“Lax laboratories: the Pap Smear Misses Much Cervical Cancer Through Lab Errors” and “Physician’s Carelessness with Pap Test is Noted in Procedure’s High Failure Rate”), Pap smear screening has been placed under intense scrutiny.¹ The fact that the Pap smear is a screening test with absolute sensitivity, specificity and predictive values has been forgotten by litigation lawyers suing successfully for the plaintiff. The line between error and negligence has become quite indiscriminate in the eyes of some litigation lawyers achieving large settlements for questionable merit. Litigation for wrongful death and decreased life expectancy for a missed invasive cancer is understandable. The case for patients with in situ cancer being awarded damages because of the delay in diagnosis means there is a chance patients may develop cervical cancer; This is a concern, particularly because of the “mental anguish” caused.¹

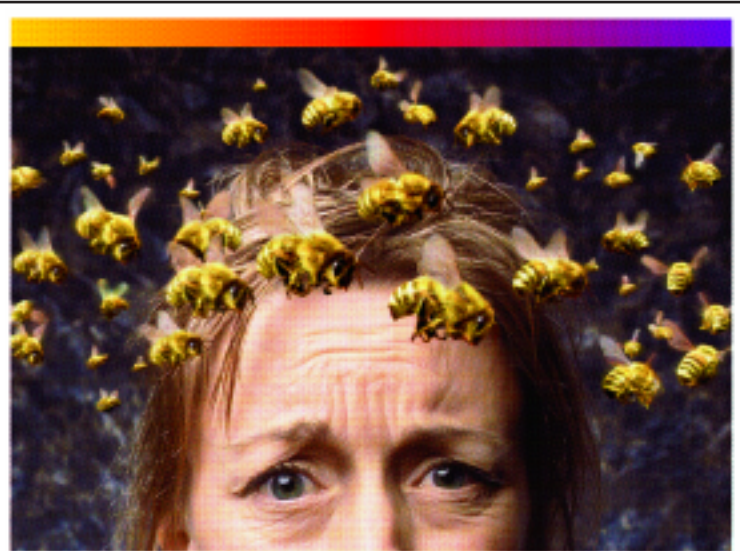
Without organized screening and stringent regulations, “Pap Mills” and abuse have occurred and the media have been swift to identify it. Enhanced quality assurance and regulations for cytology laboratories have resulted.

Current Pap smear laboratory standards limit slide review to a maximum of 100 slides per 24 hours by an individual. There is mandatory rescreening of 10% of normal results, and high grade or worse Pap smears trigger a review of all Pap smears for that patient for the past five years. Laboratory statistics, cytologic and histologic correlation are all reviewed to standard.¹ A lab is expected to review a minimum of 15,000 slides

per year to maintain its expertise and acumen in cytologic review.

Evaluations of Pap smears can be very difficult particularly if the smear has blood, exudate, clumping or other artifacts. There is well documented inter- and intra-observer variability given time of day, background information and other factors. A zero standard is impossible. An irreducible 5% to 10% false-negative rate of cancer or SIL in previously-screened smears exists. This rate increases to 10% to 20% if you include ASCUS and LSIL. Most importantly, however, a major error is rare.

Given such a climate of growing misunderstanding and unrealistic expectations for the Pap smear as more than a screening test, improvements to the process or replacement testing options are being sought out.



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Practice Pointer

Providing a good sample for the lab can help ensure the Pap smear test results are accurate. Here are some pointers:

- Take the sample halfway through the patient's menstrual cycle (when there is no blood present).
- Tell your patient not to use creams, douches, contraceptives or other preparations for three days prior to the test.
- Tell patients not to engage in sexual intercourse in the 24 hours preceding the test.

New technologies

New technologies address the failure to detect abnormalities that exist at the time of screening. These errors can be divided into sampling errors (one third) and detection errors (two thirds).

New tools for evaluation of cervical cytology are expected to achieve a diagnostic performance exceeding that of conventional Pap testing. The aim is to increase the detection of HSIL, decrease false-negatives and decrease misclassification of those without pathology. How is this now being done?

Improvement in Sample Preparation: The conventional cytology specimens are prepared by smearing the cells from the transformation zone onto one slide without clumping, as even as possible. The slide is then sprayed with fixative to prevent air drying, stained in the lab and reviewed manually under 10x magnification at 2 mm intervals. There are 30,000 to 500,000 cells on a Pap smear slide.¹ An innovation to improve the cell sample distribution is liquid-based cytology. The ThinPrep and AutoCyte Prep systems were approved to address the "sampling" concerns about Pap smears. Instead of smearing the sample cells onto a slide, the practitioner suspends them into a medium and the suspension is sent to the lab, where it is filtered or centrifuged to remove blood and debris. The remaining cells are then evenly distributed on the slide as a monolayer which is available for review. The tech-

nology is meant to prevent clumping and overlapping, which can possibly obscure abnormal cells not visible to the viewer.

Computer Review: The errors associated with interpretation of the cells on the slide have been addressed through computerized systems. PAPNET uses neural-network technology to interpret computerized images of the Pap slide. The system identifies cells based on preset criteria that require review and creates a summary display of up to 128 images. The cytotechnologist still reviews the images and can return to the original slide for correlation. The AutoPap 300QC system similarly uses algorithms to identify slides for rescreening based on a pre-selected probability for containing abnormal cells. The system does not point out the abnormal cells. The user can set the system at different thresholds that will result in 10%, 15% and 20% review rates. The AutoCyte Screen system presents images to a human reviewer who then determines whether a manual review is required. The "human" opinion is then compared to the computer generated probability opinion. If either the computer or the human says an abnormality is present, then the cytotechnologist is required to review for a determination of the abnormality.^{16,17}

Human Papillomavirus (HPV) Testing: The latest refinement for HPV testing is the Hybrid Capture 2 which detects 13 high-risk HPV subtypes. HPV testing can be combined with the ThinPrep as the excess media can be used for HPV testing. Through chemiluminescence of antibody-bound DNA-RNA hybrids of HPV, its presence and viral load can be quantified.¹⁷

Evidence-based outcomes of the new technologies

The Agency for Health Care Policy and Research (AHCPR) authors, in collaboration with the

Research Triangle Institute/University of North Carolina, systematically reviewed the quality and diagnostic performance of the new technologies. Of 962 articles reviewed, 199 included the new technology. Unfortunately, none of the studies met the criteria to base any conclusions. The problems encountered included lack of a reference standard for biopsy-proven histology for correlation, or analysis of populations that were not comparable to a general population that would be screened. The studies failed to define adequately the test characteristics of sensitivity, predictive values and effectiveness. There was no data available to assess long-term benefit if the tests were implemented in screening systems with intervals and repeat screening. Precise determination of the costs, outcomes and potential harms of using the different approaches could not be made, however, some general trends and conclusions are evolving.¹⁶

Sampling and Computer Technologies: Brown and colleagues performed a cost-effectiveness (CE) analysis to evaluate the new technologies in comparison to standard Pap smear screening. They estimated costs based on a hypothetical cohort of 25 to 65-year-old women. The ThinPrep and computerized technologies increased the cost per woman screened by \$30 to \$257 and life expectancy by five hours to 1.6 days. The screening interval affected the cost per life year saved. For example, the cost per life year saved rose from \$7,777 with screening every four years to \$166,000 with annual screening. As another reference point, the CE of conventional Pap every three years, compared with no Pap, was \$4,079 per life-year saved. Addition of new technology every three years had an incremental cost of \$22,010 which was still less than an acceptable threshold level established at \$50,000 per life year saved.¹⁴

Another way of looking at this for the primary-care physician is to consider the clinical implications of such tests in one's own practice. In the US, 0.03% of Pap smears show invasive cancer, 0.6% have HSIL, 2.5% have LSIL. Using conditional probabil-

Practice Pointer

HPV testing is being evaluated as a potential useful triage of women with borderline lesions.

- Studies have shown test sensitivity to be 90+% but the false positive rate is 5 to 20%.
- The potential value for HPV testing resides in identifying low risk women who test negative for HPV over the age of 35;
- The major problem with HPV status is the inability to discriminate between HPV positive women who will go on to get severe dysplasia versus those that won't.

ity calculations applied to ThinPrep, 19 additional women will be identified with HSIL over standard cytology. In doing so, 532 additional women will be identified with LSIL. For every case of HSIL, 28 cases of LSIL will need to be dealt with for follow-up.¹⁶ Given the natural history of progression and regression of these lesions, many more women potentially may be alarmed needlessly and overtreated. The excess cost of detecting, following up, and possibly treating these lower risk cases is significant.

HPV Testing: HPV testing is being evaluated as a potential useful triage of women with borderline lesions. The ASCUS/LSIL study group evaluated 3,600 women identified with ASCUS and 3,600 women with LSIL. 83% of LSIL had HPV. The HPV test was not found to be useful for LSIL slide triage, however there may be benefit in the triage of ASCUS lesions. Studies have shown test sensitivity to be 90+% but the false positive rate is 5% to 20%. Kaufman found no advantage of HPV testing over repeat Pap followup as a result of nine studies that used Hybrid Capture 2.

The potential value for HPV testing resides in identifying low-risk women over the age of 35 who

Pap smear

test negative for HPV. Their screening may be less frequent. The major problem with HPV status is the inability to discriminate between HPV-positive women who will go on to get severe dysplasia versus those that do not. Many women will experience a high-risk HPV infection and will never go on to severe dysplasia or cancer.²⁰ In young women, who may have a transitory HPV manifestation, many will have an abnormality detected during cytology, such as ASCUS or LSIL, which may regress. There is a potential for overtreatment.

On the Horizon

Genetic predisposition for dysplasia and cancer, and susceptibility for the virus to exert its oncogenic potential are being reviewed. Population studies have been done looking for genetic predisposition for cervical dysplasia and cancer. Although some genetic variants may appear more common, such studies are still in their infancy and a genetic link for cervical cancer is one of many diseases now being investigated following the abundance of genetic research. Molecular markers are also being evaluated for the staining of Pap smears to better elucidate and identify potential abnormalities that may be missed among the cells of a sample slide. These are not yet in clinical studies or use. A review of the Internet sites reveals a plethora of new capital ventures for cervical screening.

How does one make sense of this information?
What are the important lessons to learn?

The concept of screening refers to the population. The patient in one's practice for whom we want the

best is the dilemma we deal with in the office every-day. Reconciling the conundrum of individual *versus* societal well-being, both physical and fiscal, is a difficult imbalance we, as physicians, juggle every-day. It is incumbent on the physician to be knowledgeable and comfortable with the quality of the cytology laboratory screening of his/her patients' smear slides. A case for centralized screening and the original recommendations of the Walton Report are still applicable.

An attempt at organizing a system of cervical screening within one's own practice, incorporating the concepts of recruitment, information systems for tracking, and adherence to regional guidelines for followup of abnormal results, is labour intensive. But if everyone starts the organization in their own area, building a significant network will follow and build momentum. Despite the many advances now evolving as an adjunct to, or to supercede, Pap smear screening, the most benefit will be derived in recruiting the silent unscreened.

"The impact of providing access to regular screening and consistent followup for patients with abnormal results is likely to be greater than implementation of these new technologies."¹⁷ [CME](#)

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Pap smear

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Suggested readings



Asthma is
a variable
disease.

