HPV Testing & Cervical Cancer Screening:

Are they linked?

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In this article:

1. **How effective is cervical cancer screening?**
2. **What is the role of HPV testing?**
3. **What HPV test should be used?**

Screening for precursor lesions of cervical cancer by the Papanicolaou (Pap) smear has been one of the greatest success stories in medicine in the past 50 years. Where cervical screening is an established part of practice, cervical cancer incidence and mortality have shown dramatic declines as a result.

Despite its triumphs, the Pap smear is far from the perfect solution. In recent years, researchers have investigated means of making cervical cancer screening more effective. These include assessing a role for human papillomavirus (HPV) testing.

What's new?

One of the major developments taking place is that the conventional smear is being replaced by a liquid-based preparation. In liquid-based cytology, the sample is placed in a liquid medium. The slide is prepared in the laboratory

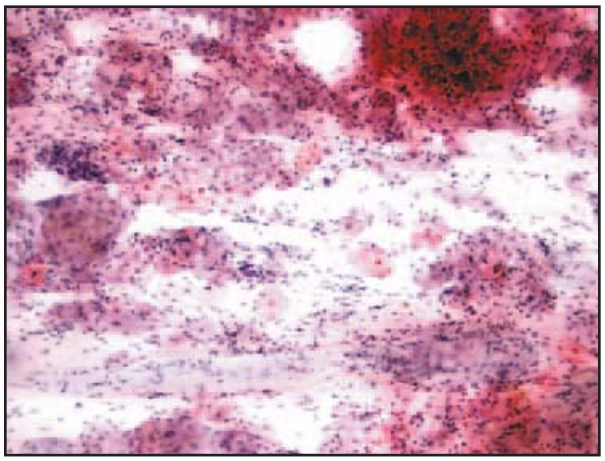

Figure 1A. This shows a conventional Pap smear with clumped, overlapped, and obscured cells mixed with inflammatory exudate and mucus.

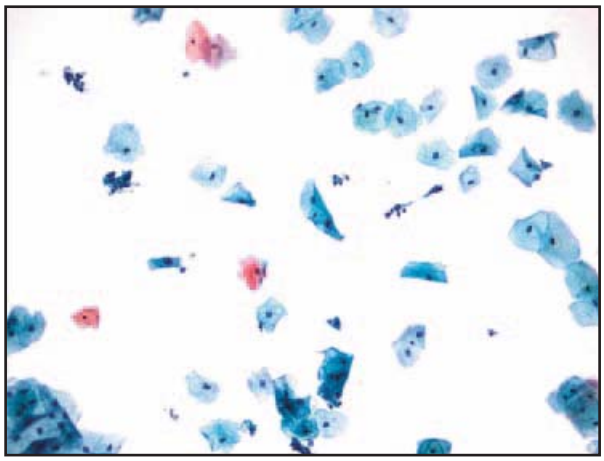

Figure 1B. This shows a liquid-based monolayer preparation illustrating well-spaced individual cells with little extraneous material.

where the cells are disaggregated, separated from extraneous material, and placed in a monolayer on the slide. The resulting preparation is of much better quality than the conventional smear, and can be interpreted with greater accuracy in less time and with less risk of false negatives due to cells being obscured by clumping or being hidden by other cells or blood (Figure 1A & 1B).

Another benefit of the liquid-based system is that only a portion of the liquid sample is used to prepare the slide, leaving the laboratory with patient material that can be used for other studies. If HPV testing is to be used, the sample can be taken from the residuum of the cytology sample rather than by recalling the patient for an additional sample.

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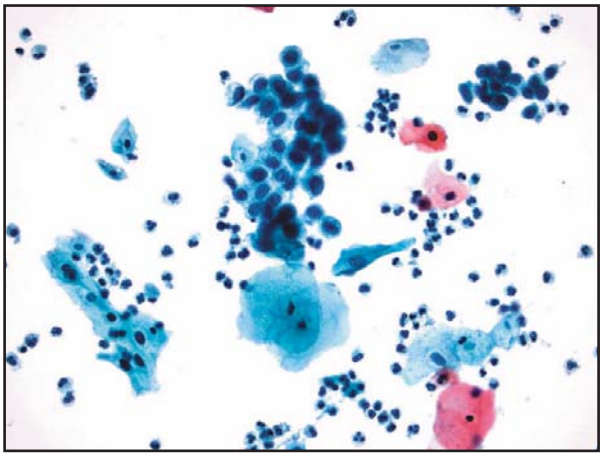

Figure 2. Cervical cells showing immature squamous metaplasia. The high nuclear cytoplasmic ratio in such cells may result in the false interpretation of a squamous intraepithelial lesion or atypical squamous cells of undetermined significance.

It is likely that within very few years most, if not all, cervical cytology in Canada will be liquid-based. That means we will not be dealing with smears at all, but with laboratory-made, machine-assisted preparations. Nevertheless, it is likely these preparations will continue to be known as "Pap smears" for many years to come.

How effective is screening?

Cervical cancer screening has had a profound positive impact on the health of women, but it is not without its shortcomings. False negatives are common. These occur either because abnormal cells, although present in the cervix, were not sampled or because abnormal cells were sampled but were obscured, overlooked, or erroneously interpreted as benign. Although the potential implications are vast, the likelihood of continued false negatives in yearly successive smears is small. For patients undergoing annual smears, the chances of missing an abnormality are extremely low. Liquid-based cytology further reduces the likelihood of false negatives because of its superior quality.

False positives are also very common and many patients with abnormal Pap smears are found, after investigation, to have no evidence of true precancerous disease. The likelihood is greater with cytologic diagnoses at the lower end of the spectrum of abnormalities, such as low grade squamous intraepithelial lesion (LSIL) or atypical squamous cells of undetermined significance (ASC-US). The reason for a high false-positive rate is that there are a variety of benign or physiologic changes in the cervix resulting in cellular changes that may be interpreted as precancerous. These changes include inflammation, which is virtually ubiquitous; squamous metaplasia, which is present in all women of reproductive age; and atrophy in post-menopausal women (Figure 2). Falsely interpreting such changes as precancerous results in unnecessary investigation and considerable anxiety and inconvenience for the patient.

Why include HPV testing?

HPV is involved in the etiology of virtually 100 per cent of cervical cancers and their precancerous states, known as squamous intraepithelial lesions (SIL). HPV can be regarded as a good marker for cervical cancer and, more specifically in the case of cervical cancer screening, cervical SIL. There are over 100 types of HPV. Of these, approximately 20 types are associated with cervical cancer and its precursors. The identification of HPV, particularly those types associated with cervical oncogenesis, could provide useful information in further establishing the true nature of disease in patients with abnormal Pap smears.

HPV testing tips

- HPV testing should be used **with** Pap smear testing, not as a replacement.
- HPV testing should only be used on patients with Pap smear abnormalities.
- Patients with latent HPV infection do not have precancerous changes in the squamous epithelial cells.
- HPV testing has the potential to reduce, but not eliminate, false positive smears.

Where does HPV testing fit?

One option for the implementation of HPV testing would be to abandon cervical cytology and make triage decisions based solely on oncogenic HPV results. Such an approach should pick up virtually all cases of SIL assuming the test being used is of near-perfect sensitivity. However, using HPV testing as a replacement to the Pap smear would identify a huge number of false positives because of the high rate of latent infection in the population. Latent infection means that HPV DNA is present but not causing disease. This is estimated to affect about 15 per cent of the adult population and there is no benefit in identifying patients with latent infection. Further investigation of all positives would flood the system with a substantially larger number of patients

HPV testing: What to consider

A significant level of concern exists that HPV testing will be used indiscriminately and for indications other than those stated in this article. It is very important to understand the implications of a positive result in a variety of settings.

Latent infections are not regarded as transmissible.

Considering the high rate of latency in the population, a positive HPV test in the absence of disease is useless information. The risk of transformation into something ominous is extremely low. The best way to minimize the risk of developing cervical cancer is to have routine Pap smears and to avoid known factors that increase the risk of progression, such as smoking.

Patients with biopsy proven SILs have an HPV infection.

Doing HPV testing once the diagnosis of SIL is established adds no additional information (however, in the laboratory, HPV testing may help to confirm the diagnosis of SIL if it is problematic in histology). It is important that patients with SIL realize the sexual contact resulting in their disease probably occurred many years earlier.

Patients with SIL are infectious and may remain infectious after treatment. Fully eliminating transmissibility in these patients is not possible, but condom use substantially reduces the risk of transmission, but does not eliminate it entirely. The transmission that does occur with condom use relates to the virus being shed from subclinical infection on squamous epithelial sites not covered by a condom. There is a myth that HPV can fit through condom pores. The reality is that latex condoms are essentially non-porous. The only condoms with pores large enough to transmit the virus are ones made of sheep gut, which are not widely used.

There is little reason to carry out HPV testing in males.

Transmission of HPV from female to male partners usually does not result in consequential disease (*i.e.,* neoplastic) in the male. The female is at a greater risk of malignancy because of the unique anatomy of the cervix with its ever-dynamic transformation zone, resulting in an area of very high vulnerability to neoplastic transformation.

HPV is equally prevalent in males and females, but the vulnerability to cancer is very different.

Management of HPV is to prevent cancer, not to reduce transmission.

No method, short of abstinence, completely eliminates HPV transmissibility. With an overall incidence rate of 15 per cent to 20 per cent (higher in younger adults), it is reasonable to concentrate efforts on cancer prevention through Pap screening and lifestyle modifications.

Take home message

HPV testing has a defined, but limited role, in cervical cancer screening. Family physicians will be providing their patients with the best care if they deal with laboratories that process liquid-based cytology and do HPV testing (particularly after HPV testing becomes paid for by the patient's insurer). As the public becomes more aware of the role of HPV in human disease, particularly cervical cancer and its precursors, physicians will need to be able to deal with questions relating to acquisition, transmission, prevention and risk of cancer. Family physicians will also need to be able to advise patients on requesting an HPV test.

for investigation than a triage system based on cytology results. It would be impractical to adopt a screening approach based solely on an HPV test.

A more practical option would be to perform HPV testing only on patients with Pap smear abnormalities. Since it is well known that many patients currently undergoing investigation for cytologic abnormalities are subsequently found to be completely normal, it makes sense that HPV testing may help to separate the true positives from the false positives. A negative HPV result in the presence of abnormal cytology is virtual confirmation of a false positive cytology result. However, a positive result is not proof of true precancerous disease because of the high frequency of latent infection. One can conclude that HPV testing has the potential to reduce, but not eliminate, false positive smears. If the reduction was substantial, implementation would be an improvement over the current situation.

Recently published consensus guidelines on managing abnormal Pap smears conclude that an HPV test

would be useful in patients with a diagnosis of ASC-US, since a negative result proves the smear to be false positive.[1] Such patients would then require no further investigation. This consensus document states that this is the only role for HPV testing and that there is no role for HPV testing in patients with negative smears. There is also no role for testing in patients with smears of greater degree of abnormality (*i.e.,* low grade or high grade SIL) than ASC-US ones since most would be expected to be positive and should be referred for further investigation.

Which HPV test should be used?

Most studies, including the ASCUS LSIL Triage Study, have used the Hybrid Capture Test. This technique identifies HPV DNA through a molecular hybridization method. It is shown to be highly sensitive and easy to perform, and as such it can be done reproducibly within routine diagnostic laboratories. Dx

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